IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

BOTTAZZI et al.

Serial No. 09/555,473

Filed: February 26, 2002

Title: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

Atty Dkt. 2801-18
C# M#
TC/A.U.: 1644
Examiner: NOLAN
Date: January 12, 2006

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

☐ **Correspondence Address Indication Form Attached.**

☐ **NOTICE OF APPEAL**
Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner twice/finally rejecting applicant's claim(s). $500.00 (1401)/$250.00 (2401) $

☒ An appeal **BRIEF** is attached in the pending appeal of the above-identified application $500.00 (1402)/$250.00 (2402) $ 500.00

☐ Credit for fees paid in prior appeal without decision on merits -$ ( )

☐ A reply brief is attached. **(no fee)**

☒ Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s)
One Month Extension $120.00 (1251)/$60.00 (2251)
Two Month Extensions $450.00 (1252)/$225.00 (2252)
Three Month Extensions $1020.00 (1253/$510.00 (2253)
Four Month Extensions $1590.00 (1254/$795.00 (2254) $ 450.00

☐ "Small entity" statement attached.

Less month extension previously paid on -$( )

TOTAL FEE ENCLOSED $ 950.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: _____

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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BOTTAZZI et al. Atty. Ref.: 2801-18

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* *

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APPEAL BRIEF

Sir:

Applicant hereby appeals the final rejection of claims 17-19, in the Office Action dated April 20, 2005, and submits the present Appeal Brief pursuant to 37 CFR § 41.37.

Table of Contents

(1) REAL PARTY IN INTEREST

The real party in interest is Sigma-Tau Industrie Farmaceutiche Riunite S.P.A., 47, Viale Shakespeare, Rome, Italy I-00144, by way of an Assignment from the appellants, recorded in the U.S. Patent and Trademark Office on May 31, 2000, at Reel 010867, Frames 0420-0421.

(2) RELATED APPEALS AND INTERFERENCES

The appellant, the appellant's legal representative, and the assignee are not aware of any related prior or pending appeals or interferences or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) STATUS OF THE CLAIMS

Claims 17-19 are pending.

Claims 17-19 have been finally rejected.

The application was originally filed with 12 claims. Originally-filed claims 9-11 were canceled and new claims 13-16 added by way of an Amendment filed November 2, 2001. Originally-filed claims 1, 3 and 5 were amended in an Amendment filed March 20, 2002. Claims 1-8 and 12-16 were canceled and 17-19 added by way of an Amendment Under Rule 116 filed November 20, 2002. The Amendment Under Rule 116 filed November 20, 2002 was entered with the filing of the Request for Continued Examination (RCE) on February 20, 2003.

No amendments to the claims have been filed in response to the Office Action dated April 20, 2005.

Claims 17-19 are the subject of the present appeal.

A copy of claims 17-19, i.e., the claims involved in the appeal, is attached as a Claims Appendix, pursuant to Rule 41.37(c)(1)(viii).

(4) STATUS OF THE AMENDMENTS

An Amendment has not been filed in response to the final Office Action dated April 20, 2005.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

The presently claimed invention provides an orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing as an active ingredient the amino acid sequence of the long pentraxin PTX3 having sequence SEQ ID NO: 1, and a pharmaceutically acceptable excipient. See independent claim 17 and originally-filed claim 1, for example. The claimed composition may also be presented in a form for the treatment of tumours, or diseases caused by bacteria, fungi, protozoa or viruses, in which the bacteria, fungi, protozoa or viruses show the capacity to bind the long pentraxin PTX3. See dependent claims 18 and 19 and originally-filed claims 4 and 5, for example,

The appellants have discovered that long pentraxin PTX3 can be used as therapeutic agents, particularly for the therapy of infectious and inflammatory diseases or tumors. As further explained below, the cited art fails to teach or suggest the presently claimed invention.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following ground of rejection is presented for review:

Whether the invention of claims 17-19 would have been obvious to one of ordinary skill in the art, under 35 U.S.C. § 103, in view of the combination of Breviario (JBC Vol. 267, No. 31, pp 22190-22197, 1992), and U.S. Patent No. 6,344,320 (Rothschild).

(7) ARGUMENT

The invention of claims 17-19 would not have been obvious to one of ordinary skill in the art in view of the combination of Breviario (JBC Vol. 267, No. 31, pp 22190-22197, 1992), and U.S. Patent No. 6,344,320 (Rothschild).

The Section 103 rejection of claims 17-19 over Breviario (JBC Vol. 267, No. 31, pp 22190-22197, 1992), and U.S. Patent No. 6,344,320 (Rothschild) should be reversed. Consideration of the following in this regard is requested.

The presently claimed invention provides an orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing as an active ingredient the amino acid sequence of the long pentraxin PTX3 having sequence SEQ ID NO: 1, and a pharmaceutically acceptable excipient. See independent claim 17 and originally-filed claim 1, for example. The claimed composition may also be presented in a form for the treatment of tumours, or diseases caused by bacteria, fungi, protozoa or viruses, in which the bacteria, fungi, protozoa or viruses show the capacity to bind the long pentraxin PTX3. See dependent claims 18 and 19 and originally-filed claims 4 and 5, for example,

The combination of cited art would not have made the claimed invention obvious to one of ordinary skill in the art. The combination of cited art would not have motivated one of ordinary skill in the art to have combined the cited references or to have made the presently claimed invention.

There is evidence of record that compositions of the art of record, including cell culture media, cell lysates and/or supernatants and other cell and protein

separation media, contain impurities and potential toxins recognized by one of ordinary skill to not be pharmaceutically acceptable and/or to have an additional pharmaceutical effect which would not be considered a pharmaceutically acceptable excipient. See De Santis Declaration executed January 8, 2004 (copy attached as Evidence Appendix (a)); and related references attached as Evidence Appendices (c)-(l).

The Examiner is understood to rely on Breviario for a teaching of PTX3. The reference is understood to provide however, at best, a putative sequence of PTX3[1], without having produced or tested the protein. There is no teaching in Breviario of a method to make PTX3.

Brevario speculates that

> "PTX3 may re[present a novel marker of inflammatory reactions, particularly those involving the vessel wall" See Abstract.

There is not teaching or suggestion of formulating PXT3 as a pharmaceutical composition or the use of PTX3 as a pharmaceutical composition. At best, Breviario may suggest that it would possibly be useful to test for the presence of PTX3 as a marker for inflammatory reactions.

The following statement in Breviario is apparently relied upon by the Examiner:

> "... the PTX3 gene reported here has characteristics that make it attractive as a potential marker for inflammatory conditions. PTX is clearly related to CRP and SAP, two classical diagnostic indicators of acute phase response."

[1] See, Figure 1 of Breviario.

> See, page 22196, right column, third to the last sentence of last paragraph, of Breviario.

Breviario does not teach or suggest a pharmaceutical formulation of the presently claimed invention.

For completeness, the appellants note that Breviario speculates that the PTX3 protein

> "is likely to be relatively unstable." See, page 22196, left column, third full paragraph, of Breviario (emphasis added).

The appellants believe that one of ordinary skill in the art would not have believed it to have been a straight-forward or reasonably predictable matter from the cited art to have made a pharmaceutical composition, as presently claimed, from a putative protein sequence, which had not been produced (according to the cited art), but which was "likely to be relatively unstable".

The Examiner admits that Breviario does not teach PTX3 in a pharmaceutical composition. See, page 2 of the Office Action of September 23, 2004.

The appellants further submit that Breviario does not suggest PTX3 in a pharmaceutical composition. The Examiner appears to be relying on Breviario to allegedly teach PTX3 in at least a solution or composition which may be a pharmaceutically acceptable solution or excipient. The Examiner appears also to be asserting that the teaching of Breviario of PTX3 as a "potential marker" may be extended, according to the Examiner, to an *in vivo* marker of "inflammatory conditions". See, page 2, last line of the Office Action of September 23, 2004.

Breviario does not suggest a pharmaceutical composition containing as an active ingredient PTX3 in a pharmaceutically acceptable excipient.

The appellants have discovered a physiological effect of PTX3 which would have been unexpected even if Breviario did teach an *in vivo* use of PTX3 as a "marker for vascular involvement in disease", which it did not. Id. Breviario does not teach a composition containing PTX3. The PTX3 protein was apparently not produced by Breviario.

The Examiner is understood to believe that the cited Rothschild patent teaches expression of "nascent proteins" in a cell free system and

> "putting said newly made proteins in pharmaceutical compositions with pharmaceutical acceptable carriers for multiple potential uses such as diagnostic kits to screen humans or other animals for the presence of certain diseases or for immunological active compositions (column 23-24 in particular). ... the ... patent allows for the translation of the newly identified protein in a pharmaceutical compositions [sic] for testing of the proteins biological properties and usefulness in a diagnostic kit or any treatment method." See, pages 2-3 of the September 23, 2004, Office Action.

As Rothschild does not teach or refer to PTX3 or any member of the pentaxin family referred to in Breviario, the Examiner is understood to believe that Rothschild would have made it obvious to have made any putative protein in a pharmaceutical composition for use in a diagnostic kit or any treatment method.

More than the cited Breviario and Rothschild are required to establish a *prima facie* case of obviousness.

The appellants believe that Rothschild teaches, as the title suggests, "**ELECTROPHORESIS**" of nascent proteins. Pentraxins are not discussed in Rothschild.

The nascent proteins of Rothschild are broadly described as follows:

> recombinant gene products, gene fusion products, enzymes, cytokines, hormones, immunogenic proteins, human proteins, carbohydrate and lipid binding proteins, nucleic acid binding proteins, viral proteins, bacterial proteins, parasitic proteins and fragments and combinations thereof. See, column 2, line 66 through column 3, line 8 of Rothschild.

Rothschild is understood to teach, in part, a method of cell free production of proteins which requires the use of detectable markers which are incorporated into the peptide chain of the protein as the protein is being produced. See, for example, column 7, lines 1-3; column 7, lines 16-21; and column 8, lines 47-48 of Rothschild.

The cell-free translation systems, which are apparently relied upon by the present Examiner, are described by Rothschild as being commercially available and as being well known. See, column 8 of Rothschild. Moreover, Rothschild describes that

> Examples of cell-free systems include prokaryotic lysates such as Escherichia coli lysates, and eukaryotic lysates such as wheat germ extracts, insect cell lysates, rabbit reticulocyte lysates, rabbit oocyte lysates and human cell lysates. Eukaryotic extracts or lysates may be preferred when the resulting protein is glycosylated, phosphorylated or otherwise modified because many such modifications are only possible in eukaryotic systems. Some of these extracts and lysates are available commercially (Promega; Madison, Wis.; Stratagene; La Jolla, Calif.; Amersham; Arlington Heights, Ill.; GIBCO/BRL; Grand

> Island, N.Y.). Membranous extracts, such as the canine pancreatic extracts containing microsomal membranes, are also available which are useful for translating secretory proteins. Mixtures of purified translation factors have also been used successfully to translate mRNA into protein as well as combinations of lysates or lysates supplemented with purified translation factors such as initiation factor-1 (IF-1), IF-2, IF-3 (.alpha. or .beta.), elongation factor T (EF-Tu), or termination factors. Id.

The cell-free translation systems of Rothschild therefore contain the same impurities that have been demonstrated by evidence in the record to not constitute a pharmaceutically acceptable excipient or solution. See attached Evidence Appendix (a) and (c)-(l).

Rothschild teaches that the nascent proteins containing the markers described by Rothschild produced in a cell-free system may be detected by separation using polyacrylamide gel electrophoresis (PAGE) and detection of the marker in the gel as an indication of the presence of the protein. See, column 11, lines 13-26 of Rothschild.

Rothschild's polyacrylamide gel containing the detectably marked nascent protein, along with other impurities, is not believed to suggest a pharmaceutical composition of the presently claimed invention, even if Rothschild did suggest detection of the putative sequence of Breviario's PTX3 sequence, which the appellants believe it did not.

Rothschild suggests use of a variety of markers, however Nε-dansyllysine and coumarin are apparently preferred. See, column 12, line 58 to column 13, line 17 of Rothschild. Rothschild teaches the possibility that the addition of the marker may

destroy the structure and function of the nascent protein containing the same. See, column 8, line 53 to column 9, line 11. Rothschild further teaches the unpredictability of inserting the marker in to the nascent protein in a manner which will preserve the structure and/or function of the nascent protein. Id.

In the passage referred to by the Examiner (i.e., columns 23 and 24 of Rothschild), the patent prophetically discusses the use of marker-containing nascent proteins with or without further purification in diagnostic or pharmaceutical compositions. Rothschild further prophetically discusses the use of toxic markers which are "therapeutically useful compounds" which are apparently targeted by the nascent protein to the site of action upon administration to a patient followed by release of the toxin by "electrical stimulation". See, column 23, lines 8-49 of Rothschild.

This description of Rothschild which is relied upon by the present Examiner is, at best, a wish to perform further research. There is no motivation in either Breviario or Rothschild to combine the references to make the presently claimed invention. There is no reasonable expectation from the cited art that, even if the references were combined, one of ordinary skill in the art would have expected to make the presently claimed invention without requiring further invention.

Rothschild further discusses the potential to use photocleavable markers as a means for removal of the

> "non-native portion of the marker to facilitate isolation of the protein in a completely native form." See, column 23, lines 50-54 of Rothschild.

Column 24 of Rothschild discusses the use of a photocleavable coumarin-biotin marker which is specifically detected using streptavidin coupled to magnetic beads.

Rothschild describes in Example 8 of the patent to cell-free production of "human IL-2" containing photocleavable-biotin (PCB)-coumarin attached to leucines of the protein. The example does not demonstrate that the PCB-coumarin-IL-2 produced is functionally active. The PCB-coumarin-IL-2 is isolated and reacted with streptavidin-coated magnetic beads, which are used to wash and resuspend the PCB-coumarin-IL-2 which is then illuminated to, apparently, remove the biotin and leave coumarin-IL-2.

The coumarin-IL-2 in the Example is then understood to be injected in mice and then collected from the same mice in serum and isolated from the serum with magnetic beads coated with an anti-coumarin antibody. The isolated bead-anti-coumarin antibody-coumarin-IL-2 was then apparently detected, and IL-2 quantitated with an antibody specific for rat IL-2 (even though human IL-2 was allegedly originally produced).

Example 8 of Rothschild, at best, demonstrates that a coumarin containing IL-2, of unknown functionality, is able to survive for a time in a mouse. Rothschild fails in Example 8 to teach even a pharmaceutical composition containing as an active ingredient IL-2 as, for example, there is no teaching that the IL-2 component of the coumarin-IL-2 was functional, or that the coumarin-IL was not detrimental to or rejected by the mouse, or that the coumarin component (i.e., the marker) of the

coumarin-IL was not functional or even acted contrary to the IL-2 in its actions or function in the mouse.

The appellants submit that the Examiner has combined the cited art with an impermissible use of hindsight. There was no motivation in the cited art to combine the references and/or to make the presently claimed invention. Even if combined, the cited art did not provide any reasonable expectation of successfully making the presently claimed invention without further experimentation. The Examiner's combination of cited art fails to establish a *prima facie* case of obviousness and, at best, establishes that it may have been obvious to try to make a composition containing the putative sequence of Breviario. Obvious to try however can not rise to the level of establishing a *prima facie* case of obviousness.

Reversal of the 35 U.S.C. § 103, rejection of claims 17-19 is requested.

The claims are submitted to be in condition for allowance and Reversal of the Final Rejection is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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(8) CLAIMS APPENDIX

17. An orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing as an active ingredient the amino acid sequence of the long pentraxin PTX3 having sequence SEQ ID NO: 1, and a pharmaceutically acceptable excipient.

18. The composition according to claims 17, for the treatment of tumours.

19. The composition according to claim 17, for the treatment of diseases caused by bacteria, fungi, protozoa or viruses, in which said bacteria, fungi, protozoa or viruses show the capacity to bind the long pentraxin PTX3.

(9) EVIDENCE APPENDIX

Attached:

(a) De Santis Declaration executed January 8, 2004

Filed with the Response Under Rule 116 filed January 16, 2004 and entered with the Request for Continued Examination (RCE) of March 16, 2004.

(b) Mantovani Declaration executed February 26, 2003

Filed with the Submission of March 10, 2003 and prior to the non-final Office Action of May 1, 2003.

(c) Federal Register Volume 63, No. 110, Tuesday, June 9, 1998, pages 31506-31513, U.S. FDA Draft Guidance on Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Entered in record by appellants with Supplemental Submission of May 13, 2004, prior to issuance of the final rejection of April 20, 2005.

(d) Herb Index (definition of Inositol) printed July 31, 2003 from the internet site blueprint.blucrossmn.com

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(e) Moore et al "Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic depressive illness" Am J Psyciatry 1999 Dec; 156(12): 1902-8 (abstract printed July 13, 2003 from internet site biosychiatry.com/myoinositol.htm)

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(f) Folic Acid information page printed July 31, 2003 from internet site suprahealth.com/folic.htm

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(g) IPCS description of Choline Chloride (1999)

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(h) Merck & Co. "Therapeutic Category and Biological Activity Index" (2002)

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(i) The Merck Manual pages 48-49 and 1600-1661, Merck & Co.

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(j) ICH Harmonised Tripartite Guideline "Stability Testing of New Drug Substances and Products Q1A(R2), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2003)

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(k) Butterworths Medical Dictionary, 2nd Edition, page 628

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(l) "Definition of Frequently Used Terms in Regulatory Affairs and Quality Assurance" Technical Reports, volume 3, number 3, Albany Molecular Research, Inc (1999)

Entered in record by appellants with Response of August 1, 2003 and listed on the PTO 1449 Form filed March 16, 2004, and considered by Examiner as indicated on initialed PTO 1449 Form dated 5/27/04.

(9) RELATED PROCEEDINGS APPENDIX

Attached:

NONE

EVIDENCE APPENDIX (a)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * * *

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

I, Rita De Santis, whose professional address is Sigma Tau SpA R&D - Immunology Area Via Pontina, Km 30.400, 00040 Pomezia – Rome, hereby declare:

1) I am presently the Head of Immunology Area at Sigma-Tau SpA - Research and Development, Pomezia, Roma, the assignee of the above-identifled application. A copy of my professional resume is attached.

2) I have reviewed the above-identified application, including the pending claims, Alles (Blood 1994, 84 (10) 8483-8493) (hereinafter "Alles") and ATCC Catalog No. 30-2002.

3) I have been advised that the U.S. Patent Office official in charge of the above-identified application believes that Alles (Blood, Volume 84, No. 10 (November 15), 1994: pages 3483-3493) provides each and every aspect of the following patent claims:

> "17. An orally, parenterally, transdermally or subcutaneously administrable pharmaceutical composition containing as an active ingredient the amino acid sequence of the long pentraxin PTX3 having sequence SEQ ID NO: 1, and a pharmaceutically acceptable excipient."
> "18. The composition according to claims 17, for the treatment of tumours."
> "19. The composition according to claim 17, for the treatment of diseases caused by bacteria, fungi, protozoa or viruses, in which said bacteria, fungi, protozoa or viruses show the capacity to bind the long pentraxin PTX3."

based on the specific disclosure at page 3485, first full paragraph, wherein I have been advised that the U.S. Patent Office official has summarized this disclosure as teaching "expressing the full-length human PTX3 protein in COS cells and incubated in DMEM and then isolating the protein in the supernatant for Western analyses." I have also been advised that the U.S. Patent Office official in charge of the above-identified application has asserted that "at the point the protein was isolated in the supernatant that had DMEM in it, the claims drawn to a pharmaceutical composition were anticipated." I have been advised that "anticipated" as used by the U.S. Patent Office official means that the official believes that each and every aspect of the above-quoted claims is taught by the Alles reference.

4) I have also been advised that the U.S. Patent Office official believes, generally, that the compositions of Alles are "pharmaceutical" compositions of the above-quoted claims.

5) I believe that one of ordinary skill in the art would believe that the Alles reference does not teach pharmaceutical compositions or pharmaceutical compositions containing pharmaceutically acceptable excipients, also containing an active ingredient of the above-quoted claims.

6) I have also been advised that the U.S. Patent Office official in charge of the above-identified application believes that one of ordinary skill in the art would believe that DMEM of Alles is a "pharmaceutically acceptable excipient".

7) I do not believe that one of ordinary skill in the art would consider DMEM of Alles to be a pharmaceutically acceptable excipient.

8) One of ordinary skill in the art will appreciate that an "excipient" is "anything other that the drug substance in the dosage form", as noted in the copy of the ICH Harmonised Tripartite Guideline, Stability Testing of New Drugs Substances in Products Q1A R(2) which I have been advised has been previously filed with the U.S. Patent Office.

9) This definition of an "excipient" is confirmed by the copy of Volume 3, No. 3 "Technical Reports" from Albany Molecular Research, Inc. "Definition of Frequently Used Terms and Regulatory Affairs and Quality Assurance" by Steven W. Fordham and Gary M. Klee, copyright 1999, which I have been advised has been previously filed with the U.S. Patent Office.

10) Moreover, page 628 from Butterworths Medical Dictionary Second Edition, McDonald Critchley, Editor–in-Chief, a copy of which I have been advised has been previously filed with the U.S. Patent Office, notes under the entry "excipients" that "excipients must not have therapeutic action on their own...".

11) I have been advised that the U.S. Patent Office official in charge of the above-identified application has also relied on ATCC Catalog No. 30-2002 for the description of DMEM and the assertion that the U.S. Patent Office official in charge of the above-identified application has asserted that this ATCC catalog reference indicates that DMEM is "useful as an in vivo solution, thereby meeting the pharmaceutical composition limitation."

12) I believe that one of ordinary skill in the art would appreciate that DMEM is not a pharmaceutically acceptable excipient.

13) It is my understanding that DMEM includes the following constituents:

- CaC12 (anhydrous);
- Fe(NO3)3-9H2O;
- MgS04 (anhydrous);
- KCl;
- NaCl;
- NaHC03;
- NaH2P04*H20;
- Choline Chloride;
- Folic Acid;
- myo-Inositol;
- Nicotinamide;

- D-Pantothenic Acid (hemicalcium);
- Pyridoxine-HCl;
- Riboflavin;
- Thiamine-HCl;
- L-Arginine-HCl;
- L-Cystine-2HCl;
- L-Glutamine;
- Glycine;
- L-Histidine-HCl-H2O;
- L-Isoleucine;
- L-Leucine;
- L-Lysine.HCl;
- L-Methionine;
- L-Phenylalanine;
- L-Serine;
- L-Threonine;
- L-Tryptophan;
- L-Tyrosine-2Na-2H2O;
- L-Valine;
- D-Glucose;
- Phenol Red, Sodium Salt; and
- Sodium Pyruvate.

14) Among the listed constituents of DMEM are the following:

Choline Chloride, Folic Acid, Myo-Inositol, Nicotinamide, D-Pantothenic Acid (hemicalcium), Pyridoxine-HCl,Riboflavin, Thiamine-HCl, L-Arginine-HClL-Cystine-2HCl, L-Glutamine, Glicine, L-Histidine-HCl-H2O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, Tyrosine-2Na-2H2O, L-Valine, Sodium Pyruvate.

15) The components listed above in ¶14) will be recognized by one of ordinary skill in the art to be drug substances such that the inclusion of the same in DMEM would lead one of ordinary skill in the art to appreciate that DMEM is not a pharmaceutically acceptable excipient, as the term is generally recognized in the art.

16) I have been advised that the following documents, which support the statement made in ¶15) above, have been previously submitted to the U.S. Patent Office and that further copies of the same are not required: page 48 of the Merck Manual which describes the use of Nicotinamide (also known as niacinamide) for treating pellagra; page 16611 of the Merck Manual which described the use of folic acid for treating coronary artery disease; excerpt from Merck's website which describes choline chloride as having a lipotropic therapeutic activity; a printout from the International Program on Chemical Safety indicating that choline chloride is a nutrient and dietary supplement with therapeutic uses; a printout from the website "suprahealth.com" indicating that folic acid has a number of therapeutic applications; a printout from the website of "biopsychiatry.com" indicating that myo-inositol has therapeutic capacity and applications; and a printout from Blue Cross also indicates that therapeutic activity of myo-inositol.

17) Beyond the above and indicated previously submitted documents, I believe one of ordinary skill in the art will appreciate that Alles does not provide pharmaceutical compositions and/or pharmaceutically acceptable excipients because, for example, the supernatant of Alles described on page 3485, first full paragraph, of Alles would not be expected to be an administerable pharmaceutical composition. More specifically, I believe one of ordinary skill in the art will appreciate that it is more likely than not that the solutions of Alles contain, for example, COS cells metabolites, catabolites and residual components of the cellular lysis, such as virus related or released by the DNA of the COS cells. One of ordinary skill in the art would appreciate therefore that even if

DMEM were a pharmaceutically acceptable excipient, which I do not believe is reasonable, the Alles document fails to provide pharmaceutical compositions.

18) I believe therefore that one of ordinary skill in the art would appreciate that the PTX3 protein described in Alles is dissolved in a solution which, more likely than not, may be toxic and/or infective such that the solution is not a pharmaceutically acceptable excipient and the composition is not adminsterable as a pharmaceutical composition.

19) Accordingly, I believe that one of ordinary skill in the art would believe that Alles fails to teach each and every aspect of the above-quoted patent claims.

20) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By [signature]
Rita De Santis

Date: January 8th, 2004

EVIDENCE APPENDIX (b)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al.

Atty. Ref.: 2801-18

Serial No. 09/555,473

Group: 1644

Filed: February 26, 2002

Examiner: Jamroz

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * * *

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION UNDER RULE 132

I, Alberto MANTOVANI, of Instituto di Ricerche Farmacologiche "Mario Negri", via Entrea 62, 20157 Milano, Italy, do hereby declare as follows:

1. I am a Professor of General Pathology at the School of Medicine, State University of Milan, Italy. A copy of my professional resume is attached.

2. I have reviewed the above-identified application and the claims.

3. I have been advised that an objection raised during the proceedings relating to the above is an alleged lack of expectation that one of ordinary skill would have been able to make and use the claimed invention, such as to treat diseases caused by bacteria, fungi, protozoa or viruses which show the capacity to bind to PTX3.

4. The following, which has been conducted by me or at my direction, is submitted as evidence that these concerns raised in the above are unfounded.

5. **PTX3 is capable to bind pathogens**

In Table 1 are reported some examples of pathogen agents which are above to bind PTX3.

TABLE 1

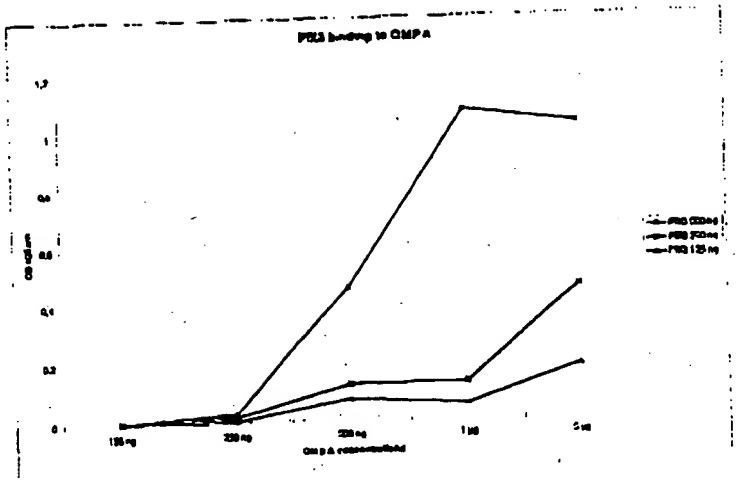
Pathogen	**Binding**
Aspergillus fumigatus	+
Pseudomonas Aeruginosa	+
Salmonella Tiphymurium	+
Staphylococcus Aureus	+

Legend: The indicated pathogens were incubated with a biotin labeled PTX3 (20 μg/ml) and analyzed b FACS with Streptavid-FITC. (+) indicate that PTX3 treated cells showed a significant increase of the mean fluorescence intensity (MFI) with respect to PTX3 untreated cells.

6. **PTX3 is capable of binding all Gram positive bacteria**

Figure 1 shows that **PTX3** is able to **bind** in vitro the outer membrane protein A (Omp A) which is expressed on the membrane surface of **all** the **Gram positive** bacteria.

Figure 1

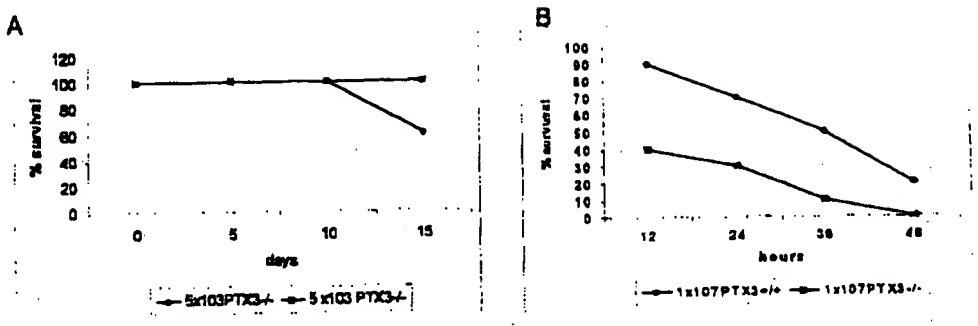


Legend: The indicated concentrations of Omp A have been absorbed on 96 multiwell plate.
Biotin labeled PTX3 at the indicated concentrations has been incubated on Omp A coated plate.
Streptavidin-HRP has been used to measure the relative amount of PTX3 bound to Omp A.

7. **Role of PTX 3 in Salmonella typhimurium and Pseudomonas aeruginosa infection**

To assess the role of PTX3 in protecting from Salmonella typhimurium and Pseudomonas aeruginosa infection, PTX3 -/- mice has been injected with the above mentioned bacteria and analyzed for survival in comparison with PTX3 +/+ mice.

Figure 2



Legend: A) The indicated doses of Salmonella Typhimurim were injected intraperitoneally in both PTX3^{+}/$^{+}$ and PTX3^{-}/$^{-}$ mice (n=8). Mortality was daily monitored. B) The indicated doses of Pseudomonas Aeruginosa were injected i.t. (intratracheally) in both PTX3^{+}/$^{+}$ and PTX3^{-}/$^{-}$ mice (n=8). Mortality was monitored every 12 hours.

The results reported in Figure 2 show that PTX3^{-}/$^{-}$ mice are more susceptible to Salmonella typhimurium and Pseudomonas aeruginosa infection then PTX3^{+}/$^{+}$ mice in terms of MST and mortality. This is a clear demonstration that PTX3 interaction with bacteria is required to protect against pathogens.

8. **Role of PTX 3 in resistance to invasive pulmonary aspergillosis**

PTX3 bound *Aspergillus fumigatus* conidia *in vitro*, this suggests a protective role for PTX3 in a murine model of invasive pulmonary aspergillosis.

PTX3 $^{-}$/$^{-}$ and $^{+}$/$^{+}$ mice were challenged with 2 x 10^{8} spores of *A. fumigatus* intratracheally. Mice were monitored for mortality, fungal load and pathology in the organs. As shown in Table 2, wild type mice survive to *A. fumigatus* in this model of infection. In contrast, in two different experiments performed, PTX 3 $^{-}$/$^{-}$ mice showed a MST of 3 days and a survival rate of 0%. *A. fumigatus* invasiveness was also assessed as fungal burden in lungs and brain. As shown in Table 2 the increased susceptibility of PTX3^{-}/$^{-}$ mice correlated with a dramatic increase in lung colonization at day three of

infection, with a 1000-fold increase in lung CFU in PTX3 $^{-/-}$ mice. The brain was not colonized in wild type mice, while in PTX 3$^{-/-}$ mice fungal burden in the brain was high (10^5 - 2 x 10^5 CFU/brain).

Mortality rate, MST and fungal burden in PTX3 $^{-/-}$ were equivalent to or worse than those obtained in PTX3 $^{+/+}$ mice after depletion of polymorphonuclear cells by treatment with anti-Gr-1 (RB6-8C5) (Table 2).

In two *in vivo* experiments PTX3$^{-/-}$ mice were treated with 20 µg of purified hPTX3 intratracheally at the time of challenge (day 0) and intravenously (day 1 and 2). As shown in Table 2 the phenotype was reverted and treated PTX3$^{-/-}$ mice behaved as PTX3$^{+/+}$ mice: mortality rate was reverted to 0/4 and MST was more than 60 days as in PTX $^{+/+}$ mice. Lung burden was reduced 4-fold by treatment. **The restoration of resistance to invasive pulmonary aspergillosis (IPA) in PTX3 $^{-/-}$ mice by PTX3 administration confirms the critical and specific role of PTX3 in this fungal infection.**

TABLE. 2- Susceptibility of PTX3 -/- mice to invasive pulmonary *aspergillosis*

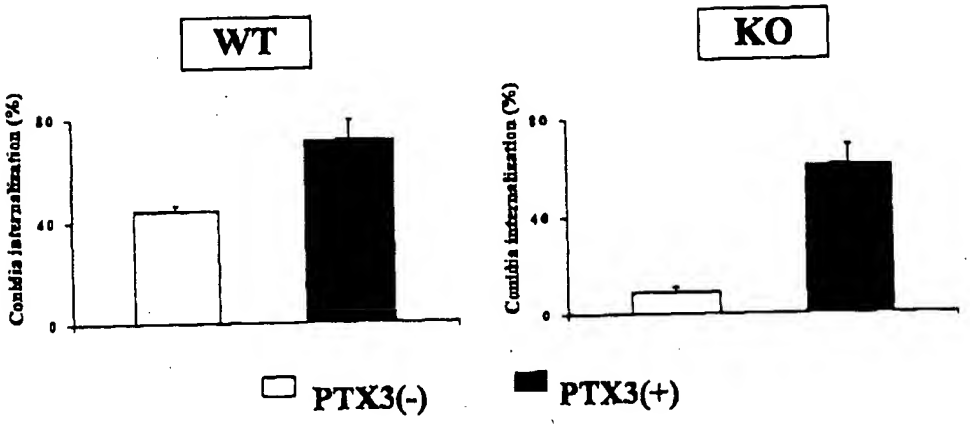
Mice	Treatment (a)	MST (days) (b)	Dead/total	Brain CFU (c)	Lung CFU (c)
Exp. 1					
PTX3 +/+	None	>60	0/3	0	8100
PTX3 +/+	RB6-8C5	4	4/4	34800	170100
PTX3 -/-	None	3	3/3	142200	706500
PTX3 -/-	RB6-8C5	3	3/3	187200	603750
Exp. 2					
PTX3 +/+	None	>60	0/6	ND	12900
PTX3 -/-	None	3	7/7	ND	233250
PTX3 -/-	PTX3*	>60	0/4	ND	60900

Legend: Mice were infected intratracheally with *A fumigatus* conidia (2 x 10^8/mouse) on day 0. (a) Mice were treated with RB6-8C5 monoclonal antibody (100 µg/mouse) intraperitoneally 2 h before fungal challenge to obtain PMN depletion or with(*) 20 µg PTX3 intratracheally on day 0 and intravenously on day 1 and 2. (b) MST: median survival time. (c) CFU were determined at day 3 after infection.

9. **PTX3 improve Phagocytosis of A. fumigatus conidia by alveolar macrophages an in vitro internalization assay.**

The ability of alveolar macrophases to ingest resting conidia in vitro, was significantly impaired in PTX3 $^{-/-}$ mice, as compared to PTX3 $^{+/+}$ mice (Fig. 3). However, PTX3 restored the phagocytic activities of cells from PTX3 $^{-/-}$ mice and potentiated PTX3 $^{+/+}$ mice (Fig. 3) This phagocytosis assay on PTX$^{+/+}$ macrophases is a further indication of the therapeutic activity of PTX3 in pulmonary infections.

Figure 3



Legend: Alveolar macrophases isolated from the indicated mice (2 x 10^5 cells/200 µl) obtained by plastic adherence from the bronchoalveolar lavage fluid, were incubated at 37° C for 2h with 10^6 conidia in 6 ml polypropylene tubes (N. 2063, Falcon), in 200 µl of Iscove medium containing 5 µg/ml polymixin B (Sigma) and 50 µl/ml gentamycin but no FCS to avoid non specific activation by serum components. Phagocytic cells were separated from non phagocytosed *A. fumigatus* cells by centrifugation on a fetal serum gradient. Harvest phagocytic cells was used for cytospin preparation. After Diff Quik staining fungal cell internalization was express according to the following formula: Conidia internalization = number of cell containing one or more fungal cells / 100 cells: In PTX3 (+), 20 µg/ml PTX 3 was added.

10. **Therapeutic function of PTX3 in a murine T-cell depleted model of invasive pulmonary asperigillosis**

Asperigillus fumigatus is a major opportunistic pathogen in immunodeficient patients and poses a formidable therapeutic challenge. It has been investigated whether administration of PTX3 was active in an invasive pulmonary aspergillosis model of allogeneic, T-cell depleted, bone marrow transplantation (BMT) in $PTX3^{+}/^{+}$ mice. As shown in Table 3, combined systemic and local PTX3 administration caused a significant two-fold increase in survival time with two out of eight mice being cured.

Moreover, the lung CFU counts were drastically reduced (> four-fold) in PTX3-treated mice.

Table 3

Mice	Treatment	MST (days)	Dead/total	Brain CFU	Lung CFU
BMT	None	3	8/8	ND	814310
BMT	PTX3*	8*	6/8	ND	187300*

Legend: Mice underwent allogeneic T-cell-depleted BMT as described in Mencacci, A. et al. *Blood* **97**, 1483-90. (2001) were infected intratracheally (i.t.) with *A fumigatus* conidia ($2x10^8$/mouse) 7 days later. PTX3 was given on day 0 i.t. and on day 1 and 2 i.v. (*, 20 µg/mouse). *$p<0.05$ compared to control mice (Mann Whitney U test).

As above mentioned:

1) PTX3 binds selected microbial agents, comprising conidia of *Asperigillus fumigatus, Pseudomonas aeruginosa, Salmonella tiphimurium, Staphylococcus aureus,* and all *Gram positive* bacteria;

2) PTX3$^{-/-}$ mice show higher mortality and reduction of the medial survival time when infected with pathogens;

3) PTX$^{-/-}$ mice infected with pathogens mentioned above show lower mortality and higher medial survival time when treated with PTX3;

4) susceptibility to *A fumigatus* infection of $^{-/-}$ mice was associated with defective recognition of conidia by alveolar macrophages and indicate that conidia opsonization by PTX3 direct binding is required to reverse defective phagocytosis; and

5) pulmonary aspergillosis infection, in a mouse model of allogeneic, T cells depleted, bone marrow transplantation can be prevented by PTX treatment thus indicating the therapeutic role of PTX3 also in $PTX3^{+/+}$ immune compromised mice.
While the applicants do not believe it necessary to indicate or explain a mechanism of action, and without wishing to be bound by any such action, the applicants believe that the data presented indicate that PTX3 works as soluble pattern recognition receptor (PRR) and is useful as protective agent in pathogens infection. In particular, PTX3 appears to be effective when bound to the pathogen agent.
This mechanism of action can be extended not only to all fungi or bacteria which are capable of binding PTX3, but also to protozoa or viruses that show the same capability to bind PTX3.

11. Accordingly, in view of the above, I believe one or ordinary skill should appreciate that the claimed invention is supported by a disclosure which teaches one of ordinary skill how to make and use the invention of the claims.

12. It is also my understanding that an objection has been raised that anti-tumor activity by cloning human PTX3 into a murine mastocytoma p815 cell line would not be expected by one of ordinary skill in the art to expect successful treatment of tumors as claimed.

13. On page 9 to page 10 line 3 of the text of the present application however, are reported data about the anticancer activity of the compound according to the present

invention: "**Anticancer activity:** a line of murine mastocytoma **P815** was transfected by electroporation with the expression vector pSG5 containing the cDNA of human PTX3 or its antisense.

Male DBA/2N CrlBR mice aged 8-10 weeks were subcutaneously injected with $1x10^5$ cells of P815 PTX3-producing clones or with clones containing the antisense gene. **The mice were monitored 3 times daily for occurrence of tumours and once daily for survival.**

The results obtained are reported in Table 2 and show the efficacy of PTX3, in this experimental model of gene therapy, in bringing about healing of the animals and complete rejection of the tumour after the take of the inoculated tumour cells.

These results are statistically significant with p<9,91 (Fisher test) both as compared to controls and to the group treated with the antisense" (Emphasis added).

On page 11, Table 2 of the text are reported the data of the antitumoral activity of the compound according to the present invention.

"**TABLE 2**	IN VIVO ANTICANCER ACTIVITY OF PTX3
Clone[1]	Reject[2]
Parent **P815** (control)	4/25
P815-AS1 (antisense)	3/8
P815-PTX3-1 (sense)	**14/14***

1: 1 x 10^5 cells of the clone indicated were injected subcutaneously.
2: Number of animals that definitely reject the tumour out of total number of animals in which it took.

*** : p<0.01 as compared both to mice treated with parent cells and to mice treated with cells of the antisense clones (Fisher test)"** (Emphasis added).

14. In view of these aspects of the disclosure, as well as the entirety of the disclosure, I believe one of ordinary skill in the art should be convinced that the above-identified specification demonstrates the antitumor activity of PTX3.

15. To further characterize the antitumor activity of PTX3 however, the murine melanoma cell line B16 was stably transfected with the palsmid vector pSG5hPTX3 encoding for human PTX3, by me or at my direction.

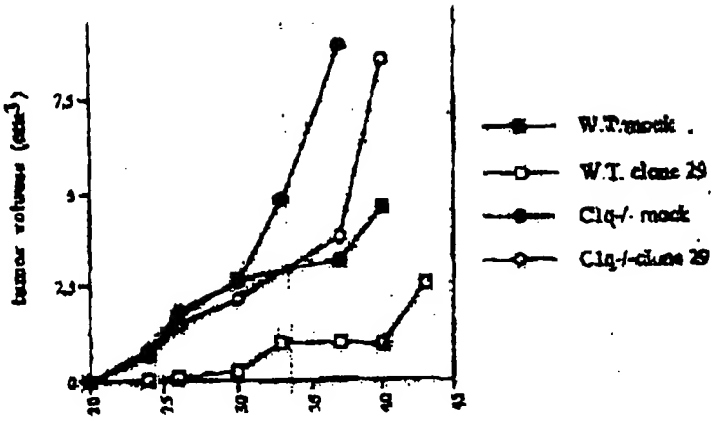
The B16 cell clone expressing the hPTX3 (PTX 29) was injected subcutaneously either in C57 mice or in C1qKO.

Untransfected B16 cells were used as control in both these mouse strains.

In the C57 mice, PTX3 transfected B16 cells showed **a significant** delay in tumor growth rate compared to untransfected parental cells (see Figure 4)

The observed delay of tumor growth rate of PTX transfected B16 cells was C1q dependant as C1q KO mice developed PTX 3 transfected and parental tumor at the same extent (see Figure 4).

Figure 4



Legend:
W.T. mock : C57/b6 mice treated subcutaneously with $1x10^5$ B16 cells;
W.T. clone 29: C57/b6 mice treated subcutaneously with $1x10^5$ B16 cells transfected with pSC5hPTX3;
C1q $^{-}\!/$ mock: C1q KO mice treated subcutaneously with $1x10^5$ B16 cells;
C1q $^{-}\!/$ clone 29: C1q KO mice treated subcutaneously with $1x10^5$ B16 cells transfected with pSG5hPTX3.

16. I believe one of ordinary skill in the art will appreciate from this evidence that the following main features characterize PTX3:

1) PTX3 is able to form a decamer by the establishment of disulfides bounds among its monomers,

2) The decamer of PTX3 is able to bind the first element of the complement classical pathway C1q (Bottazzi et al. 1997).

The experiment shown in Figure 4 highlight the antitumor activity of PTX3 even in the context of the B16 melanoma cell line and indicate that decamerization and C1q binding capacity of PTX3 is required for its antitumor activity.

17. The data reported in the application as filed and these above further presented data are a clear demonstration and confirmation of the antitumoral activity of the compound according to the invention.

18. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, declarant sayeth not.

Signed _____ Date 26/2/03
Alberto MANTOVANI

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Form No.	21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
Form FDA 356 V	514.1 and 514.8	180	8.78	1,824	211.8	271,694
	514.8 and 514.9				30	8,520
	514.11				1	1,824
Total burden hours						282,038

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

The estimate of the burden hours required for reporting are based on fiscal year 1998 data. The burden estimate includes original NADA's, supplemental NADA's, and amendments to unapproved applications.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc 98-15271 Filed 6-8-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Request for Nominations for Members on Public Advisory Committees; Veterinary Medicine Advisory Committee

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting nominations for members to serve on the Veterinary Medicine Advisory Committee (the Committee) in FDA's Center for Veterinary Medicine.

FDA has a special interest in ensuring that women, minority groups, and the physically challenged are adequately represented on advisory committees and, therefore, extends particular encouragement to nominations for appropriately qualified candidates from these groups.

DATES: No cutoff date is established for receipt of nominations.

ADDRESSES: All nominations for membership should be submitted to Jacquelyn L. Pace (address below).

FOR FURTHER INFORMATION CONTACT: Jacquelyn L. Pace, Center for Veterinary Medicine (HFV-200), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-6650.

SUPPLEMENTARY INFORMATION: FDA is requesting nominations for members to serve on the Committee. The function of the Committee is to review and evaluate available data concerning safety and effectiveness of marketed and investigational new animal drugs, feeds, and devices for use in the treatment and prevention of animal disease and increased animal production.

Criteria for Members

Persons nominated for membership on the Committee shall have adequately diversified experience that is appropriate to the work of the Committee in such fields as companion animal medicine, food animal medicine, avian medicine, microbiology, biometrics, toxicology, pathology, pharmacology, animal science, public health/epidemiology, minor species/minor use veterinary medicine, and chemistry. The specialized training and experience necessary to qualify the nominee as an expert suitable for appointment is subject to review, but may include experience in medical practice, teaching, and/or research relevant to the field of activity of the Committee. The term of office is 4 years.

As of November 1, 1998, the Committee will have three vacancies in the areas of animal science, veterinary toxicology, and veterinary microbiology. However, membership nominations are not limited to these three areas.

Nomination Procedures

Any interested person may nominate one or more qualified persons for membership on the Committee. Nominations shall state that the nominee is willing to serve as a member of the Committee and appears to have no conflict of interest that would preclude committee membership. A current copy of the nominee's curriculum vitae should be included. Potential candidates will be asked by FDA to provide detailed information concerning such matters as employment, financial holdings, consultancies, and research grants or contracts in order to permit evaluation of possible sources of conflict of interest.

This notice is issued under the Federal Advisory Committee Act (5 U.S.C. app. 2) and 21 CFR part 14, relating to advisory committees.

Dated: May 29, 1998.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 98-15195 Filed 6-8-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D-0374]

International Conference on Harmonisation; Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guidance entitled "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products." The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guidance provides guidance on general principles for the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. The draft guidance is intended to assist in the establishment of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

DATES: Written comments by July 24, 1998

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Copies of the draft guidance are available from the Drug Information Branch (HFD-210), Center for Drug

Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573. Single copies of the guidance may be obtained by mail from the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), or by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800. Copies may be obtained from CBER's FAX Information System at 1-888-CBER-FAX or 301-827-3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Neil D. Goldman, Center for Biologics Evaluation and Research (HFM-20), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-0377.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In February 1998, the ICH Steering Committee agreed that a draft guidance entitled "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" should be made available for public comment. The draft guidance is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group.

The draft guidance provides guidance on general principles for the selection of test procedures and the setting and justification of acceptance criteria for biotechnological and biological products. The draft guidance is intended to assist in the establishment of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

This draft guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological/biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may, on or before July 24, 1998, submit to the Dockets Management Branch (address above) written comments on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this draft guidance is available on the Internet at "http://www.fda.gov/cder/guidance/index.htm" or at CBER's World Wide Web site at "http://www.fda.gov/cber/publications.htm".

The text of the draft guidance follows:

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products[1]

Table of Contents

1.0 Introduction

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of their manufacture should conform to be considered acceptable for their intended use.

[1] This draft guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for biotechnological/biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

"Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are proposed and justified by the manufacturer, and approved by regulatory authorities.

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which many of the specifications are based, a validated manufacturing process, raw materials testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

1.1 Objective

This guidance document provides guidance on general principles for the setting and justification, to the extent possible, of a uniform set of international specifications for biotechnological/biological products to support new marketing applications.

1.2 Scope

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types, such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides/polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components.

This document does not recommend specific test procedures or acceptance criteria that should be established for the proposed value, nor does it apply to the regulation of preclinical and/or clinical research material.

2.0 General Principles for Consideration in Setting Specifications

2.1 Characterization

Characterization of a biotechnological/biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) is necessary to allow relevant specifications to be established. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical/clinical studies, data from lots used for demonstration of manufacturing consistency, and relevant development data, such as those arising from analytical procedures and stability studies.

Extensive characterization usually is performed only in the development phase and, where necessary, following significant process changes. At the time of submission, the product should have been compared with an appropriate reference standard, if available. When feasible and relevant, it should be compared with its natural counterpart. Also, at the time of submission, the manufacturer should have established appropriately characterized in-house reference materials (primary and working) which will serve for biological assay and physicochemical testing of production lots.

2.1.1 Physicochemical properties

A physicochemical characterization program will generally include a determination of the composition, physical properties, and primary structure of the desired product. In some cases, information regarding higher-order structure of the desired product (the fidelity of which is generally inferred by its biological activity) may be obtained by appropriate physicochemical methodologies.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated post-translationally modified forms (e.g., glycoforms). These forms may be active and their presence has no deleterious effect on the safety and efficacy of the product (section 2.1.4). The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical/clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity, efficacy, and safety (including immunogenicity) of individual forms may not be necessary.

Heterogeneity can also be produced during manufacture and/or during storage of the drug substance or drug product. Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterized to ensure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they are considered product-related substances. When process changes and degradation products result in heterogeneity patterns that differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated.

Analytical methods to elucidate physicochemical properties are listed in appendix 6.1. New analytical technology and modifications to existing technology are continually being developed. Such technologies should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

2.1.2 Biological activity

Assessment of the biological properties constitutes an equally essential step in establishing a complete characterization profile. An important property is the biological activity which describes the specific ability or capacity of a product to achieve its intended biological effect.

A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include:

- Animal-based biological assays, which measure an organism's biological response to the product;
- Cell culture-based biological assays, which measure biochemical or physiological response at the cellular level; and
- Biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunological interactions.

Other procedures, such as ligand/receptor binding assays, may be acceptable.

Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product that is linked to the relevant biological properties, whereas quantity (expressed in mass) is a physicochemical measure of protein content. Although mimicking the biological activity in the clinical situation is not necessary, a correlation between the expected clinical response and the activity in the biological assay should be established.

The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized. Where no such reference standard exists, a characterized "in-house" reference material should be established and assay results of production lots reported as "in-house" units.

Often, for complex molecules, the physicochemical information may be extensive but unable to confirm the higher order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure. Importantly, a biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where:

- Sufficient physicochemical information about the drug, including higher order structure, can be thoroughly established by such physicochemical methods, and relevant correlates to biologic activity demonstrated; and
- There exists a well-established manufacturing history.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

For the purpose of lot release (section 4), the choice of relevant quantitative assay (biological and/or physicochemical) should be justified by the manufacturer.

2.1.3 Immunochemical properties

When an antibody is the desired product, its immunological properties should be fully

characterized. Binding assays of the antibody to purified antigens and defined regions of antigens should be performed, as feasible, to determine affinity, avidity, and immunoreactivity (including cross-reactivity). In addition, the target molecule bearing the relevant epitope should be biochemically defined and the epitope itself defined, when feasible.

For some drug substances/drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., ELISA, Western Blot) utilizing antibodies that recognize different epitopes of the protein molecule. Immunochemical properties of a protein may serve to establish its identity, homogeneity, or purity, or serve to quantify it.

If immunochemical properties constitute lot release criteria, all relevant information pertaining to the antibody should be made available.

2.1.4 Purity, impurities, and contaminants

- *Purity*

The determination of absolute, as well as relative, purity presents considerable analytical challenges, and the results are highly method-dependent. Historically, the relative purity of a biological product has been expressed in terms of specific activity (units of biological activity per milligram of product), which is also highly method-dependent. Consequently, the purity of the drug substance and drug product is assessed by a combination of analytical procedures.

Due to the unique biosynthetic production process and molecular characteristics of biotechnological/biological products, the drug substance can include several molecular entities or variants. When these molecular entities are derived from anticipated post-translational modification, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and have properties comparable to the desired product, they are considered product-related substances and not impurities (see section 2.1.1).

Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.

For the purpose of lot release (section 4), an appropriate subset of methods should be selected and justified for determination of purity.

- *Impurities*

In addition to evaluating the purity of the drug substance/drug product—which may be composed of the desired product and multiple product-related substances, the manufacturer should also assess impurities which may be present. Impurities may be either process- or product-related. They can be of known structure, partially characterized, or unidentified. When adequate quantities of impurities can be isolated, the identity of these materials should be determined as a minimum requirement and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, i.e., derived from the culture (e.g., inducers, antibiotics, or media components) or from downstream processing (see appendix section 6.2.1). Product-related impurities (e.g., certain degradation products) are molecular variants arising from processing or during storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Further, the acceptance criteria for impurities should be based on data obtained for lots used in preclinical and clinical studies and manufacturing consistency lots.

Individual and/or collective acceptance criteria for impurities (product-related and process-related) should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary (section 2.3).

Examples of analytical procedures that may be employed to test for the presence of impurities are listed in appendix 6.2. New analytical technology and modifications to existing technology are continually being developed. Such technologies should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

- *Contaminants*

Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical/biochemical materials (e.g., microbial proteases) and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits or drug substance/drug product specifications (see section 2.3). For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in ICH guidances Q5A "Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" and Q5D "Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" should be considered.

2.1.5 Quantity

Quantity, usually measured as protein content, is critical for a biotechnological/biological product and should be determined using an appropriate assay, usually physicochemical in nature. In some cases, it may be demonstrated that the quantity values obtained may be directly related to those found using the biological assay. When this correlation exists, it may be appropriate to use measurement of quantity rather than measurement of biological activity to determine manufacturing parameters, such as for filling.

2.2 Analytical Considerations

2.2.1 Reference standards and reference materials

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities, and process-related impurities may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability should also be provided.

2.2.2 Validation of analytical procedures

At the time the application is submitted to the regulatory authorities, applicants should have validated the analytical procedures used in the specifications in accordance with the ICH guidances Q2A "Validation of Analytical Procedures: Definitions and Terminology" and Q2B "Validation of Analytical Procedures: Methodology," except where there are specific issues for unique tests used for analyzing biotechnological/biological products.

2.3 Process Controls

2.3.1 Process-related considerations

Adequate design of a process and knowledge of its capability are part of the strategy used to develop a manufacturing process that is controlled and reproducible, yielding a drug substance/drug product which meets specifications. In this respect, limits are justified based on critical information gained from the entire process spanning the period from early development through commercial-scale production.

For certain impurities, testing on either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies. This can include verification at commercial-scale in accordance with regional regulations. It is recognized that only limited data may be available at the time of submission of an application. This concept may, therefore, sometimes be implemented after marketing authorization, in accordance with regional regulations.

2.3.2 In-process acceptance criteria and action limits

In-process tests are performed at critical decision making steps and at points where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The in-process test results may be recorded as action limits or reported as acceptance criteria. Monitoring for the presence of mycoplasma and adventitious virus at the end of a cell culture harvest and/or other stages is an example of testing for which in-process acceptance criteria should be set. Performing

such testing may eliminate the need for testing of the drug substance/drug product (section 2.3.1).

The use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer, should be further refined as increased experience and data are obtained after product approval.

2.3.3 Raw materials and excipient specifications

The quality of the raw materials used in the production of the drug substance (or drug product) should meet acceptable standards, appropriate for their intended use. Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures that make use of affinity chromatography (for example, employing monoclonal antibodies) should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance/drug product. Appropriate information pertaining to the antibody should be made available.

The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.

2.4 Pharmacopoeial Specifications

Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria which, where relevant, are part of the evaluation of either the drug substance or drug product. Such monographs, applicable to biotechnological/biological products, generally include, but are not limited to, tests for sterility, endotoxins, bioburden, volume in container, uniformity of dosage forms, and particulate matter. With respect to the use of pharmacopoeial methods and acceptance criteria, the value of this guidance is linked to the extent of harmonization of the analytical procedures of the pharmacopoeias. The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

2.5 Release Limits Versus Shelf-Life Limits

The concept of release limits versus shelf-life limits may be applied where justified. This concept pertains to the establishment of limits which are tighter for the release than for the shelf-life of the drug substance/drug product. Examples where this may be applicable include potency and degradation products. In some regions, the concept of release limits may only be applicable to in-house limits and not to the regulatory shelf-life limits.

2.6 Statistical Concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

3.0 Justification of the Specification

The setting of specifications for drug substance and drug product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation/validation, stability testing, and testing for consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

- Specifications are linked to a manufacturing process.

Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities, and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns which differ from those observed in the material used during preclinical and clinical development. The significance of these alterations should be evaluated.

- Specifications should account for the stability of drug substance and drug product.

Degradation of drug substance and drug product, which may occur during storage, should be considered when establishing specifications. Due to the inherent complexity of these products, there is no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of which tests should be included will be product-specific. The manufacturer is referred to the ICH guidance Q5C "Stability Testing of Biotechnological/Biological Products."

- Specifications are linked to preclinical and clinical studies.

Specifications should be based on data obtained for lots used in preclinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.

- Specifications are linked to analytical procedures.

Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities. Such attributes can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, it is not unusual for the analytical technology to evolve in parallel with the product. Therefore, it is important to confirm that data generated during development correlate with those generated at the time the marketing application is filed.

4.0 Specifications

Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical/clinical studies, lots used for demonstration of manufacturing consistency, and relevant development data, such as those arising from analytical procedures and stability studies.

In some cases, testing at production stages rather than testing the finished drug substance or drug product may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and included in the specification of drug substance or drug product in accordance with the requirements of the regional regulatory authorities.

4.1 Drug Substance Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug substances. Pharmacopoeial tests (e.g., endotoxin detection) should be performed on the drug substance, where appropriate. Additional drug substance specific acceptance criteria may also be necessary.

4.1.1 Appearance/description

A qualitative statement describing the physical state (e.g., solid, liquid) and color of a drug substance should be provided.

4.1.2 Identity

The identity test(s) should be specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity. The identity test(s) for a drug substance can be qualitative in nature and, generally, need not be highly sensitive. Some of the methods typically used for characterization of the product as described in section 2.1 and in appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

4.1.3 Purity and impurities

Since the absolute purity of biotechnological/biological products is difficult to determine and the results are method-dependent (section 2.1.4), the purity of the drug substance is usually estimated by a combination of methods.

The impurities observed in these products are classified as process-related and product-related:

- Process-related impurities (section 2.1.4) in the drug substance may include culture media, host cell proteins, DNA,

monoclonal antibodies and chromatographic media used in purification, solvents/buffer components. These impurities should be minimized by the use of appropriate well-controlled manufacturing processes.

• Product-related impurities (section 2.1.4) in the drug substance are molecular variants with properties different from those of the desired product resulting from processing or from storage.

The choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities. Individual and/or collective acceptance criteria for impurities should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary.

4.1.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biological/biotechnological drug substance and/or drug product. When an appropriate potency assay is used for the drug product, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage (section 4.2.4). In some cases, the measurement of specific activity may provide additional useful information.

4.1.5 Quantity

The quantity of the drug substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be reference standard/material independent. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

4.2 Drug Product Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug products. Each section (4.2.1–4.2.5) is cross referenced to respective sections (4.1.1–4.1.5) under Drug Substance Specification. Pharmacopoeial requirements apply to the relevant dosage forms. Typical tests found in the pharmacopoeia include, but are not limited to, sterility, endotoxin, microbial limits, volume in container, particulate matter, uniformity of dosage forms, and moisture content for lyophilized drug products. If appropriate, testing for uniformity of dosage form may be performed as in-process controls and corresponding acceptance criteria are set.

4.2.1 Appearance/description

A qualitative statement describing the physical state (e.g., solid, liquid), color, and clarity of the drug product should be provided.

4.2.2 Identity

The identity test(s) should be specific for the drug product and should be based on unique aspects of its molecular structure and other specific properties. The identity test(s) can be qualitative in nature and generally need not be highly sensitive. While it is recognized that in most cases a single test is adequate, more than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity for some products. Some of the methods typically used for characterization of the product as described in section 2.1 and in appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

4.2.3 Purity and impurities

Impurities may be generated or increase in the manufacture of the drug product. These may be either the same as those occurring in the drug substance itself, process-related, or degradation products which form specifically in the drug product during formulation or during storage. If impurities are qualitatively and quantitatively (i.e., relative amounts and/or concentrations) the same as in the drug substance, testing is not considered necessary. If impurities are known to be introduced or formed during the production of the drug product, the levels of these impurities should be determined and acceptance criteria established.

Acceptance criteria and analytical procedures should be developed and justified, based upon previous experience with the drug product, to measure changes in the drug substance during the manufacture of the drug product.

The choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from excipients and impurities including degradation products inherent in the drug product.

4.2.4 Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biological/biotechnological drug substance and/or drug product. When an appropriate potency assay is used for the drug substance, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product (section 4.1.4).

4.2.5 Quantity

The quantity of the drug substance in the drug product, usually based on protein content, should be determined using an appropriate assay. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

4.2.6 General tests

Physical description and the measurement of other quality attributes are often important for the evaluation of the drug product functions. Examples of such tests include pH and osmolarity.

4.2.7 Additional testing for unique dosage forms

It should be recognized that certain unique dosage forms may need additional tests other than those mentioned above.

5.0 Glossary

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance which the drug substance or drug product or materials at other stages of their manufacture should meet to conform with the specification of the results of analytical procedures.

Action limits: An action limit is an internal (in-house) value used to assess the consistency of the process at less critical steps. These limits are the responsibility of the manufacturer.

Biological activity: Biological activity describes the specific ability or capacity of the product to achieve its intended biological effect. Potency is the quantitative measure of the biological activity.

Contaminants: Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) in the drug substance/drug product not intended to be part of the manufacturing process.

Degradation products: Degradation products are molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of processing and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

Desired product: The protein that is expected from the DNA sequence and anticipated post-translational modifications (including glycoforms) and intended downstream processing necessary to produce an active biological molecule.

Drug product (Dosage form; Finished product): A pharmaceutical product type that contains a drug substance, generally in association with excipients.

Drug substance (Bulk material): The drug substance is the material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients and other components, such as buffers.

Excipient: An ingredient added intentionally to the drug product or drug substance which should not have pharmacological properties in the used quantity.

Impurity: Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient (including added buffer components). It may be either process- or product-related.

Potency: Potency is the measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties.

Process-related impurities: Impurities that are derived from the manufacturing process. They may be derived from cell substrates, culture (e.g., inducers, antibiotics, or media components), or from downstream processing (e.g., processing reagents or column leachables).

Product-related impurities: Product-related impurities are molecular variants of the desired product arising from processing or during storage (e.g., certain degradation products) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Product-related substances Product-related substances are molecular variants of the desired product which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

Raw material: Raw material is a collective name for substances or components used in the manufacture of the drug substance or drug product.

Reference standards/materials: In addition to the existing international/national standards, it is usually necessary to create in-house reference materials

— In-house primary reference material: A primary reference material is an appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

— In-house working reference material: The in-house working reference material is a material prepared similarly to the primary reference material and is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

Specification: A specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria for the tests described, which establishes the set of criteria to which a drug substance or drug product or materials at other stages of their manufacture should conform to be considered acceptable for its intended use.

6.0 Appendices

6.1 Appendix for Physicochemical Characterization

This appendix provides examples of technical approaches which might be considered for structural characterization/confirmation and evaluation of physicochemical properties of the desired product. The specific technical approach employed will vary from product to product, and alternative approaches, other than those included in this appendix, will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed. Such technologies should be utilized when appropriate.

6.1.1 Structural characterization/confirmation

(a) Amino acid sequence

The amino acid sequence of the desired product should be determined to the extent possible using approaches such as those described in items (b) through (e) and then compared with the sequence of the amino acids deduced from the gene sequence of the desired product.

(b) Amino acid composition

The overall amino acid composition is determined using various hydrolytic and analytical procedures and compared with the amino acid composition deduced from the gene sequence for the desired protein, or the natural counterpart, if considered necessary, taking into account the size of the molecule. In many cases, amino acid composition analysis provides some useful structural information for peptides and small proteins, but such data are generally less definitive for large proteins. Quantitative amino acid analysis data can also be used to determine protein content in many cases.

(c) Terminal amino acid sequence

Terminal amino acid analysis is performed to identify the nature and homogeneity of the amino (N-) and carboxy (C)-terminal amino acids. If the desired product is found to be heterogeneous with respect to the terminal amino acids, the relative amounts of the variant forms should be determined using an appropriate analytical procedure. The sequence of these terminal amino acids should be compared with the terminal amino acid sequence deduced from the gene sequence of the desired protein.

(d) Peptide map

Selective fragmentation of the product into discrete peptides is performed using suitable enzymes or chemicals, and the resulting peptide fragments are analyzed by HPLC or other appropriate analytical procedures. The peptide fragments should be identified to the extent possible using techniques such as amino acid compositional analysis, N-terminal sequencing, or mass spectrometry. Validated peptide mapping is frequently an appropriate method to confirm desired product structure/identity for lot release purposes.

(e) Sulfhydryl group(s) and disulfide bridges

If, based on the gene sequence for the desired protein, cysteine residues are expected, the number and positions of any free sulfhydryl groups and/or disulfide bridges should be determined, to the extent possible. Peptide mapping (under reducing and nonreducing conditions), mass spectrometry, or other appropriate techniques may be useful for this evaluation

(f) Carbohydrate structure

For glycoproteins, the carbohydrate content (neutral sugars, amino sugars, and sialic acid) is determined. In addition, the structure of the carbohydrate chains, the oligosaccharide pattern (antennary profile), and the glycosylation site(s) of the polypeptide chain are analyzed, to the extent possible.

6.1.2 Physicochemical properties

(a) Molecular weight/size

Molecular weight (or size) is determined using size exclusion chromatography, SDS-polyacrylamide gel electrophoresis (under reducing and/or nonreducing conditions), mass spectrometry, and/or other appropriate techniques.

(b) Isoform pattern

This is determined by isoelectrical focusing or other appropriate techniques.

(c) Extinction coefficient (or molar absorptivity)

In many cases, it will be desirable to determine the extinction coefficient (or molar absorptivity) for the desired product at a particular UV/visible wavelength (e.g., 280 nanometers). The extinction coefficient is determined using UV/visible spectrophotometry on a solution having a known protein content as determined by techniques such as amino acids compositional analysis or nitrogen determination.

(d) Electrophoretic patterns

Electrophoretic patterns and data on identity, homogeneity, and purity of the desired product/drug substance obtained by polyacrylamide gel electrophoresis, isoelectric focusing, SDS-polyacrylamide gel electrophoresis, Western-Blot, capillary electrophoresis, or other suitable procedures are determined as appropriate.

(e) Liquid chromatographic patterns

Chromatographic patterns and data on the identity, homogeneity, and purity of the desired product/drug substance obtained by size exclusion chromatography, reverse-phase liquid chromatography, ion-exchange liquid chromatography, affinity chromatography, or other suitable procedures are determined as appropriate

(f) Spectroscopic profiles

The ultraviolet and visible absorption spectra are determined as appropriate. The higher-order structure of the product is examined using procedures such as circular dichroism, nuclear magnetic resonance (NMR), or other suitable techniques as appropriate.

6.2 Appendix for Impurities

This appendix lists potential impurities, their sources, and examples of relevant analytical approaches for detection. Specific impurities and technical approaches employed, as in the case of physicochemical characterization, will vary from product to product, and alternative approaches other than those listed in this appendix will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed. Such technologies should be utilized when appropriate.

6.2.1 Process-related impurities

These are derived from the manufacturing process (section 2.1.4) and are classified into three major categories: Cell substrate-derived, culture-derived, and downstream-derived.

(a) Cell substrate-derived impurities include proteins/polypeptides derived from the host organism; nucleic acid (host cell genetic/vector/total DNA); polysaccharides; viruses. For host cell proteins, a sensitive immunoassay capable of detecting a wide range of protein impurities is generally utilized. The polyclonal antibody utilized in the test is generated from a crude preparation of a mock production organism, i.e., a production cell minus the product-coding gene. The level of DNA from host cells can be detected by direct analyses on the product (such as hybridization techniques) and/or by spiking experiments (laboratory scale) demonstrating the removal of nucleic acid by the purification process. For intentionally introduced viruses, the ability of the manufacturing process to remove/inactivate viruses should be demonstrated as described in the ICH guidance Q5A "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin."

(b) Culture-derived impurities include inducers (polynucleotides, viruses) antibiotics, serum, other media components.

(c) Downstream-derived impurities include enzymes, chemical/biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidizing and reducing agents), inorganic salts (e.g., heavy metals, arsenic, non metallic ion), solvents, carrier/ligands (e.g., monoclonal antibodies), other leachables.

6.2.2 Product-related impurities

The following represents the most frequently encountered molecular variants of the desired product and lists relevant technology for their assessment:

(a) Truncated forms. Cellular peptidases may catalyze the removal of amino acids or catalyze internal cleavages. This may be detected by HPLC or SDS-PAGE. Peptide mapping may be useful, depending on the property of the variant.

(b) Deamidated, isomerized, mismatched S-S linked, oxidized forms may need considerable effort in isolation and characterization in order to identify the type of chemical modification(s) and amino acid residue(s) involved. Chromatographic and/or electrophoretic methods (e.g., HPLC, capillary electrophoresis, mass spectroscopy, circular dichroism) may be utilized to isolate and characterize such variants.

(c) The category of aggregates includes dimers and higher multiples of the molecular entity. These are generally resolved from the active moiety and quantitated by size exclusion chromatography (e.g., SE-HPLC). Degradants identified from stability studies as being generated in significant amounts should be tested for and monitored against appropriately established acceptance criteria.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98N-0285]

Sanofi Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 21 New Drug Applications and 62 Abbreviated New Drug Applications; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a document that appeared in the Federal Register of May 12, 1998 (62 FR 26191). The document announced the withdrawal of approval of 21 new drug applications (NDA's) and 62 abbreviated new drug applications (ANDA's). The document was published with an error in the identification of NDA for Pipanol Powder and Tablets (trihyphenidyl) held by Sanofi Pharmaceuticals, Inc. This document corrects that error.

EFFECTIVE DATE: June 11, 1998.

FOR FURTHER INFORMATION CONTACT: Olivia A. Pritzlaff, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

In FR Doc. 98-12613, appearing on page 26191 in the Federal Register of Tuesday, May 12, 1998, the following correction is made:

On page 26191, in the table, in the first column, the first entry "NDA 4-496" is corrected to read "NDA 7-796".

Dated: June 3, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98-15338 Filed 6-8-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0532]

Agency Information Collection Activities; Announcement of OMB Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled "Radioactive Drug Research Committee (RDRC) Report on Research Use of Radioactive Drug Membership Summary and Radioactive Drug Research Use of Radioactive Drug Study Summary" has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA).

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Information Resources Management (HFA-250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1482.

SUPPLEMENTARY INFORMATION: In the Federal Register of January 9, 1998 (63 FR 1484), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under section 3507 of the PRA (44 U.S.C. 3507). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910-0053. The approval expires on May 31, 2001.

Dated: June 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98-15191 Filed 6-8-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[HCFA-1044-N]

Medicare Program; June 22, 1998, Meeting of the Practicing Physicians Advisory Council

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice of meeting.

SUMMARY: In accordance with section 10(a) of the Federal Advisory Committee Act, this notice announces a meeting of the Practicing Physicians Advisory Council. This meeting is open to the public.

DATES: The meeting is scheduled for June 22, 1998, from 8:30 a.m. until 5 p.m., E.S.T.

ADDRESSES: The meeting will be held in Room 800, 8th Floor, Hubert H. Humphrey Building, 200 Independence Avenue, SW, Washington, DC 20201.

FOR FURTHER INFORMATION CONTACT: Aron Primack, MD, MA, FACP, Executive Director, Practicing Physicians Advisory Council, Room 435-H, Hubert H. Humphrey Building, 200 Independence Avenue, S.W., Washington, DC 20201, (202) 690-7874.

SUPPLEMENTARY INFORMATION: The Secretary of the Department of Health and Human Services (the Secretary) is mandated by section 1868 of the Social Security Act to appoint a Practicing Physicians Advisory Council (the Council) based on nominations submitted by medical organizations representing physicians. The Council meets quarterly to discuss certain proposed changes in regulations and carrier manual instructions related to physicians' services, as identified by the Secretary. To the extent feasible and consistent with statutory deadlines, the consultation must occur before publication of the proposed changes. The Council submits an annual report on its recommendations to the Secretary and the Administrator of the Health

EVIDENCE APPENDIX (d)

Inositol (Vitamin B8)

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Below:

Introduction

Inositol, unofficially referred to as "vitamin B_8," is present in all animal tissues, with the highest levels in the heart and brain. It is part of the membranes (outer linings) of all cells, and plays a role in helping the liver process fats as well as contributing to the function of muscles and nerves.

Inositol may also be involved in depression. People who are depressed have much lower-than-normal levels of inositol in their spinal fluid. In addition, inositol participates in the action of *serotonin,* a neurotransmitter known to be a factor in depression. (Neurotransmitters are chemicals that transmit messages between nerve cells.) For this reason, inositol has been proposed as a treatment for depression, and preliminary evidence suggests that it may be helpful.

Inositol has also been tried for other psychological and nerve-related conditions.

Sources

Inositol is not known to be an essential nutrient. However, nuts, seeds, beans, whole grains, cantaloupe, and citrus fruits supply a substance called phytic acid (inositol hexaphosphate, or IP6), which releases inositol when acted on by bacteria in the digestive tract. The typical American diet provides an estimated 1,000 mg daily.

Therapeutic Dosages

Experimentally, inositol dosages of up to 18 g daily have been tried for various conditions.

Therapeutic Uses

Some but not all studies suggest that high-dose inositol may be useful for depression.[1-4]

Inositol has also been studied for bipolar disorder,[5] panic disorder,[6,7] bulimia,[8] and obsessive-compulsive disorder,[9,10] but the evidence remains far from conclusive. Other potential uses include Alzheimer's disease[11] and attention deficit disorder.[12]

Inositol is also sometimes proposed as a treatment for complications of diabetes, specifically diabetic neuropathy, but there have been no double-blind placebo-controlled studies, and two uncontrolled studies had mixed results.[13,14]

Inositol has also been investigated for potential cancer-preventive properties.[15-22]

What Is the Scientific Evidence for Inositol?

Depression

Small double-blind studies have found inositol helpful for depression.[23,24] In one such trial, 28 depressed individuals were given a daily dose of 12 g of inositol for 4 weeks.[25] By the fourth week, the group receiving inositol showed significant improvement compared to the placebo group.

A double-blind study of 42 people with severe depression that was not responding to standard antidepressant treatment found no improvement when inositol was added.[26]

Panic Disorder

People with panic disorder frequently develop panic attacks, often with no warning. The racing heartbeat, chest pressure, sweating, and other physical symptoms can be so intense that they are mistaken for a heart attack. A small double-blind study (21 participants) found that people given 12 g of inositol daily had fewer and less severe panic attacks as compared to the placebo group.[27]

A double-blind crossover study of 20 individuals compared inositol to the antidepressant drug fluvoxamine (Luvox), a medication related to Prozac.[28] The results over 4 weeks of treatment showed that the supplement was at least as effective as the drug.

Safety Issues

No serious ill effects have been reported for inositol, even with a therapeutic dosage that equals about 18 times the average dietary intake. However, no long-term safety studies have been performed.

Although inositol has sometimes been recommended for bipolar disorder, there is evidence to suggest inositol may trigger manic episodes in people with this condition.[29] If you have bipolar disorder you should not take inositol unless under a doctor's supervision.

Safety has not been established in young children, women who are pregnant or nursing, and those with severe liver and kidney disease. As with all supplements used in multigram doses, it is important to purchase a reputable product, because a contaminant present even in small percentages could add up to a real problem.

References

1. Levine J, Barak Y, Kofman O, et al. Follow-up and relapse analysis of an inositol study of depression. *Isr J Psychiatry Relat Sci.* 1995;32:14-21.

2. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

3. Benjamin J, Agam G, Levine J, et al. Inositol treatment in psychiatry. *Psychopharmacol Bull.* 1995;31:167-175.

4. Nemets B, Mishory A, Levine J, et al. Inositol addition does not improve depression in SSRI

treatment failures. *J Neural Transm.* 1999;106:795-798.

5. Chengappa KN, Levine J, Gershon S, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disord.* 2000;2:47-55.

6. Benjamin J, Levine J, Fux M, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry.* 1995;152:1084-1086.

7. Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21:335-339.

8. Gelber D, Levine J, Belmaker RH. Effect of inositol on bulimia nervosa and binge eating. *Int J Eat Disord.* 2001;29:345-348.

9. Fux M, Levine J, Aviv A, et al. Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry.* 1996;153:1219-1221.

10. Fux M, Benjamin J, Belmaker RH. Inositol versus placebo augmentation of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: a double-blind cross-over study. *Int J Neuropsychopharmcol.* 1999;2:193-195.

11. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

12. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

13. Salway JG, Finnegan JA, Barnett D, et al. Effect of myo-inositol on peripheral-nerve function in diabetes. *Lancet.* 1978;2:1282-1284.

14. Gregersen G, Bertelsen B, Harbo H, et al. Oral supplementation of myoinositol: effects on peripheral nerve function in human diabetics and on the concentration in plasma, erythrocytes, urine and muscle tissue in human diabetics and normals. *Acta Neurol Scand.* 1983;67:164-172.

15. Wattenberg LW. Chemoprevention of pulmonary carcinogenesis by myo-inositol. *Anticancer Res.* 1999;19:3659-3661.

16. Dong Z, Huang C, Ma WY. PI-3 kinase in signal transduction, cell transformation, and as a target for chemoprevention of cancer. *Anticancer Res.* 1999;19:3743-3747.

17. Yang GY, Shamsuddin AM. IP6-induced growth inhibition and differentiation of HT-29 human colon cancer cells: involvement of intracellular inositol phosphates. *Anticancer Res.* 1995;15:2479-2487.

18. Ishikawa T, Nakatsuru Y, Zarkovic M, et al. Inhibition of skin cancer by IP6 in vivo: initiation-promotion model. *Anticancer Res.* 1999;19(5A):3749-3752.

19. Shamsuddin AM. Metabolism and cellular functions of IP6: a review. *Anticancer Res.* 1999;19 (5A):3733-3736.

20. Shamsuddin AM, Vucenik I. Mammary tumor inhibition by IP6: a review. *Anticancer Res.* 1999;19 (5A):3671-3674.

21. Vucenik I, Kalebic T, Tantivejkul K, et al. Novel anticancer function of inositol hexaphosphate: inhibition of human rhabdomyosarcoma in vitro and in vivo. *Anticancer Res.* 1998;18(3A):1377-1384.

22. Shamsuddin AM, Vucenik I, Cole KE. IP6: a novel anti-cancer agent. *Life Sci.* 1997;61:343-354.

23. Levine J, Barak Y, Kofman O, et al. Follow-up and relapse analysis of an inositol study of depression. *Isr J Psychiatry Relat Sci.* 1995;32:14-21.

24. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

25. Benjamin J, Agam G, Levine J, et al. Inositol treatment in psychiatry. *Psychopharmacol Bull.* 1995;31:167-175.

26. Nemets B, Mishory A, Levine J, et al. Inositol addition does not improve depression in SSRI treatment failures. *J Neural Transm.* 1999;106:795-798.

27. Benjamin J, Levine J, Fux M, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry.* 1995;152:1084-1086.

28. Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21:335-339.

29. Levine J, Witztum E, Greenberg BD, et al. Inositol-induced mania? [letter]. *Am J Psychiatry.* 1996;153:839.

Reviewed By HealthGate CAM Medical Review Board

First published May 12, 2000
Last updated March 1, 2002

Printer-friendly version

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of the Health On the Net Foundation

EVIDENCE APPENDIX (e)

Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic-depressive illness

by

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***Am J Psychiatry* 1999 Dec; 156(12):1902-8**

ABSTRACT

OBJECTIVE: The most widely accepted hypothesis regarding the mechanism underlying lithium's therapeutic efficacy in manic-depressive illness (bipolar affective disorder) is the inositol depletion hypothesis, which posits that lithium produces a lowering of myo-inositol in critical areas of the brain and the effect is therapeutic. Lithium's effects on in vivo brain myo-inositol levels were investigated longitudinally in 12 adult depressed patients with manic-depressive illness. METHOD: Medication washout (minimum 2 weeks) and lithium administration were conducted in a blinded manner. Regional brain myo-inositol levels were measured by means of quantitative proton magnetic resonance spectroscopy at three time points: at baseline and after acute (5-7 days) and chronic (3-4 weeks) lithium administration. RESULTS: Significant decreases (approximately 30%) in myoinositol levels were observed in the right frontal lobe after short-term administration, and these decreases persisted with chronic treatment. The severity of depression measured by the Hamilton Depression Rating Scale also decreased significantly over the study. CONCLUSIONS: This study demonstrates that lithium administration does reduce myo-inositol levels in the right frontal lobe of patients with manic-depressive illness. However, the acute myo-inositol reduction occurs at a time when the patient's clinical state is clearly unchanged. Thus, the short-term reduction of myo-inositol per se is not associated with therapeutic response and does not support the inositol depletion hypothesis as originally posited. The hypothesis that a short-term lowering of myo inositol results in a cascade of secondary signaling and gene expression changes in the CNS that are ultimately associated with lithium's therapeutic efficacy is under investigation.

OCD
SAMe

Cannabis
Kava-kava
Hyperforin
Moodfoods
Herbal highs
Lithium at 50
St John's wort
Inositol depletion
Goldfish on inositol
Inositol and depression
Inositol as an antidepressant
Lithium maintenance: review

Refs
HOME
HedWeb
Future Opioids
BLTC Research
Paradise-Engineering
Utopian Pharmacology
The Hedonistic Imperative
When Is It Best To Take Crack Cocaine?

EVIDENCE APPENDIX (f)

Folic Acid

(folate, folacin)

FOLIC ACID: Information on folic acid (folate, folacin).

RDA or AI for Adults

- Non-pregnant adults: 400 mcg; During pregnancy: 600 mcg (Prevents some birth defects.)

Adult Maintenance - Therapeutic Range

- 200 - 1,000 mcg. (At high doses, balance with extra vitamin B12.)

Major Sources

- Green leafy vegetables, organ meats (liver), lean beef, wheat, eggs, fish, dry beans, lentils, cowpeas, asparagus, broccoli, collards, yeast. Synthesized by intestinal bacteria.

Non-Therapeutic Importance

- Appears essential for biosynthesis of nucleic acids; essential for normal maturation of red blood cells; functions as the coenzyme, tetrahydrofolic acid.

Deficiency Symptoms

- Confusion
- Depression
- Diarrhea
- Fatigue
- Megaloblastic anemia

Increased Risk for Deficiency

- Alcoholism
- Anorexia
- Anticonvulsant drugs
- Diverticulosis
- Elderly
  Hemolytic anemias

-
- Malabsorption diseases
- Malignancies
- Oral contraceptive agents
- Pregnancy and lactation
- Vitamin B12 deficiency

Possible Therapeutic Applications

CONSULT WITH A HEALTH PROFESSIONAL FIRST: Folic acid works with vitamin B12 in reducing homocysteine, a risk factor for heart disease. Supplementation *may* prevent, correct deficiencies caused by, or be helpful with, the following conditions:

- Acne
- Acquired Immunodeficiency Syndrome (AIDS, HIV)
- Aging
- Alcoholism
- **Atherosclerosis (heart disease)**
- Cancer
- Cardiac Arrhythmias
- Cataracts
- **Celiac Disease**
- **Cerebrovascular Disease (including stroke)**
- Chronic Fatigue Syndrome (CFS, CFIDS)
- Constipation
- **Crohn's Disease**
- Eating Disorders (anorexia, bulimia)
- Gout
- Hypercholesterolemia (high cholesterol)
- Immunodepression (immune function)
- Infection (colds, flu, etc.)
- Infertility (female)
- Infertility (male)
- Intermittent Claudication (poor circulation)
- Irritable Bowel Syndrome (IBS)
- **Memory Loss (Alzheimer's disease, dementia)**
- Multiple Sclerosis (MS)
- **Osteoarthritis**
- Osteoporosis
- Periodontal Disease
- Psoriasis
- Rheumatoid Arthritis
- **Ulcerative Colitis**

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CHOLINE CHLORIDE

0853
October 1995

CAS No: 67-48-1
RTECS No: KH2975000
UN No:
EC No:

(2-Hydroxyethyl)trimethylammonium chloride
Choline hydrochloride
2-Hydroxy-N,N,N-trimethylethanaminium chloride
Cholinium chloride
$C_5H_{14}NO.Cl$
Molecular mass: 139.6

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Water spray, powder.
EXPLOSION			
EXPOSURE			
Inhalation		Ventilation.	Fresh air, rest.
Skin		Protective gloves.	Rinse and then wash skin with water and soap.
Eyes		Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting.	Symbol R: S:

EMERGENCY RESPONSE	STORAGE

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS TO WHITE HYGROSCOPIC CRYSTALS.

Occupational Exposure Limits
TLV not established. MAK not established.

Routes of Exposure
The substance can be absorbed into the body by ingestion.

Inhalation Risk
No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of Short-term Exposure
See Notes.

Effects of Long-term or Repeated Exposure
Repeated or prolonged contact may cause skin sensitization.

PHYSICAL PROPERTIES

Boiling point (decomposes): 247°C

Solubility in water: miscible

ENVIRONMENTAL DATA

NOTES

The substance is a plant growth inhibitor factor, a nutrient, a dietary supplement and has therapeutic uses. Few data available.

ADDITIONAL INFORMATION

THERAPEUTIC CATEGORY AND BIOLOGICAL ACTIVITY INDEX

LAXATIVE/CATHARTIC *(continued)*

Seidlitz Mixture, *8499*
Senna, *8528*
Sennosides, *8529*
Sodium Phosphate, Dibasic, *8733*
Sodium Succinate, *8754*
Sodium Sulfate, *8755*
Sodium Tartrate, *8759*
Sorbitol, *8797*
Sulisatin, *9073*

LEUKOTRIENE ANTAGONIST *see also Antiasthmatic*

Ibudilast, *4904*
Montelukast, *6281*
Pranlukast, *7795*
Zafirlukast, *10162*

LH-RH AGONIST *see also Antineoplastic; Gonad-Stimulating Principle*

Buserelin, *1491*
Deslorelin, *2940*
Goserelin, *4541*
Histrelin, *4743*
Leuprolide, *5478*
Nafarelin, *6377*
Triptorelin, *9818*

LH-RH ANTAGONIST *see also Antineoplastic*

Cetrorelix, *2036*
Ganirelix, *4380*

LIPOTROPIC

N-Acetylmethionine, *98*
Choline Chloride, *2226*
Choline Dehydrocholate, *2227*
Choline Dihydrogen Citrate, *2228*
Inositol, *5001*
Lecithin, *5447*
Methionine, *6004*

5-LIPOXYGENASE INHIBITOR *see also Antiallergic; Antiasthmatic; Anti-inflammatory; Antipsoriatic*

Amlexanox, *490*
Lonapalene, *5586*
Tenidap, *9221*
Zileuton, *10178*

LOCAL ANESTHETIC *see Anesthetic (Local)*

LUPUS ERYTHEMATOSUS SUPPRESSANT

Bismuth Sodium Triglycollamate, *1281*
Chloroquine, *2182*
Hydroxychloroquine, *4843*

MAJOR TRANQUILIZER *see Antipsychotic*

MATRIX METALLOPROTEINASE INHIBITOR

Batimastat, *1011*
Prinomastat, *7840*

MINERALOCORTICOID

Aldosterone, *224*
Deoxycorticosterone, *2917*
Deoxycorticosterone Acetate, *2918*
Fludrocortisone, *4156*

MINOR TRANQUILIZER *see Anxiolytic*

MIOTIC

Carbachol, *1786*
Neostigmine, *6492*
Physostigmine, *7469*
Pilocarpine, *7505*

MONOAMINE OXIDASE INHIBITOR *see also Antidepressant; Antihypertensive; Antiparkinsonian*

Befloxatone, *1022*
Iproclozide, *5095*
Iproniazid, *5097*
Isocarboxazid, *5174*
Lazabemide, *5411*
Moclobemide, *6247*
Mofegiline, *6253*
Octamoxin, *6781*
Pargyline, *7110*
Phenelzine, *7300*
Phenoxypropazine, *7342*
Pivalylbenzhydrazine, *7595*
Prodipine, *7857*
Selegiline, *8502*
Toloxatone, *9599*
Tranylcypromine, *9649*

MUCOLYTIC

Acetylcysteine, *90*
Bromhexine, *1375*
Carbocysteine, *1812*
Domiodol, *3448*
Erdosteine, *3677*
Letosteine, *5468*
Lysozyme, *5660*
Mecysteine Hydrochloride, *5809*
Mesna, *5936*
Sobrerol, *8638*
Stepronin, *8887*
Tiopronin, *9532*
Tyloxapol, *9901*

MUSCLE RELAXANT (SKELETAL) *see also Neuromuscular Blocking Agent*

Afloqualone, *183*
Baclofen, *939*
Botulin Toxins, *1345*
Carisoprodol, *1854*
Chlormezanone, *2122*
Chlorphenesin Carbamate, *2197*
Chlorzoxazone, *2214*
Cyclobenzaprine, *2742*
Dantrolene, *2842*
Diazepam, *3018*
Eperisone, *3637*
Idrocilamide, *4917*
Inaperisone, *4952*
Mephenesin, *5875*
Mephenoxalone, *5876*
Methocarbamol, *6010*
Mivacurium Chloride, *6240*
Orphenadrine, *6945*
Phenprobamate, *7343*
Pridinol Mesylate *see 7830*
Quinine, *8151*
Tetrazepam, *9315*
Thiocolchicoside *see 9398*
Tizanidine, *9561*
Tolperisone, *9600*

MUSCLE RELAXANT (SMOOTH) *see Antimuscarinic*

MYDRIATIC

Atropine, *879*
Cyclodrine, *2748*
Cyclopentolate, *2775*
Epinephrine, *3650*
Eucatropine, *3930*
Homatropine, *4750*
Hydroxyamphetamine, *4835*
Phenylephrine Hydrochloride, *7370*
Scopolamine, *8481*
Tropicamide, *9850*
Yohimbine, *10157*

NARCOTIC ANALGESIC *see Analgesic (Narcotic)*

NARCOTIC ANTAGONIST

Amiphenazole, *483*
Cyclazocine, *2733*
Levallorphan, *5479*
Nalmefene, *6386*
Nalorphine, *6387*
Naloxone, *6388*
Naltrexone, *6389*

NASAL DECONGESTANT *see Decongestant*

NEURAMINIDASE INHIBITOR *see also Antiviral*

Oseltamivir, *6958*
Zanamivir, *10167*

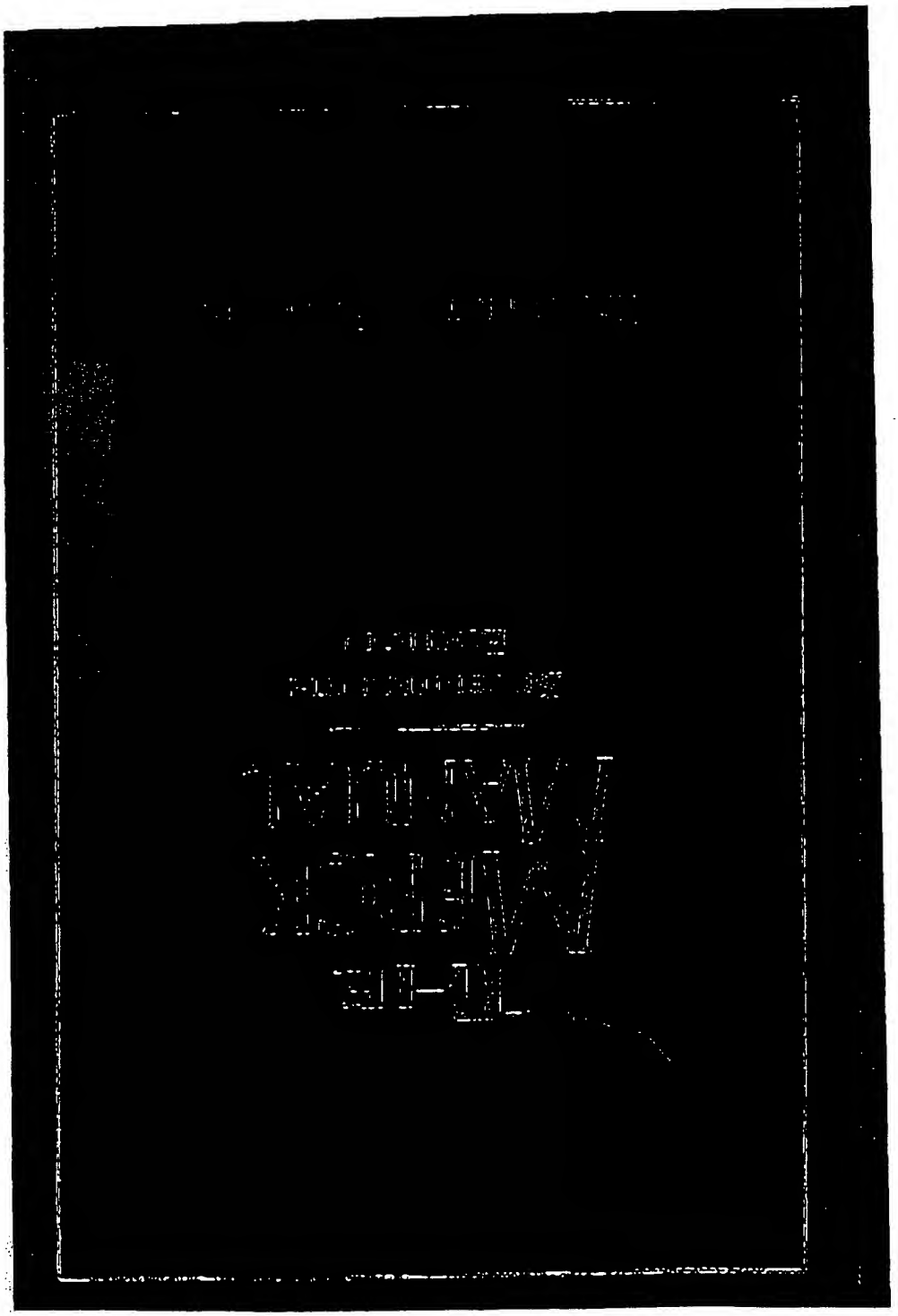
NEUROLEPTIC *see Antipsychotic*

NEUROMUSCULAR BLOCKING AGENT

Depolarizing Agents

Decamethonium Bromide, *2867*
Succinylcholine Bromide, *8958*
Succinylcholine Chloride, *8959*
Succinylcholine Iodide, *8960*

EVIDENCE APPENDIX (i)



Pellagra

pigmented over pressure points, secondary infection often develops, and the lesion has a sharply defined pearly border of regenerating epithelium when healing begins

- Chronic atrophic lesions, with dry, scaly, inelastic skin too large for the part it covers (seen in older pellagrins).

The distribution of lesions—at trauma points—is more characteristic than their form. Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

Mucous membrane symptoms primarily affect the mouth but may also affect the vagina and urethra. Scarlet glossitis and stomatitis are characteristic of acute deficiency. The tip and margins of the tongue and the mucosa around Stensen's duct are affected first. As the lesion progresses, the entire tongue and oral mucous membranes become bright scarlet, followed by a sore mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth. They are often covered by a grayish slough containing Vincent's organisms.

GI symptoms, which are indeterminate in early cases, include burning of the mouth, pharynx, and esophagus and abdominal discomfort and distention. Later, nausea, vomiting, and diarrhea may occur. Diarrhea, often bloody because of GI hyperemia and ulceration, is serious.

CNS symptoms include organic psychosis, characterized by memory impairment, disorientation, confusion, and confabulation (excitement, depression, mania, and delirium predominate in some patients; in others, the reaction is paranoid); and (2) encephalopathic syndrome, characterized by clouding of consciousness, cogwheel rigidity of the extremities, and uncontrollable sucking and grasping reflexes. Differentiating these CNS changes from those in thiamine deficiency is difficult.

Diagnosis and Treatment

Niacin deficiency must be distinguished from other causes of stomatitis, glossitis, diarrhea, and dementia. Diagnosis is easy when the clinical findings include skin and mouth lesions, diarrhea, delirium, and dementia. More often, the condition is less fully developed, and a history of a diet lacking niacin and tryptophan is significant. Urinary excretion of N'-methylnicotinamide (NMN) and its pyridone is decreased. NMN excretion of < 0.8 mg/day suggests a niacin deficiency.

Multiple deficiencies of B vitamins and protein often occur together, therefore, a balanced diet is needed. Supplemental niacinamide 300 to 1000 mg/day should be given orally in divided doses. In most cases, 300 to 500 mg is sufficient. Niacinamide is generally used to treat deficiency states, because niacin can cause flushing, itching, burning, or tingling sensations, whereas niacinamide does not; however, niacinamide does not possess hypolipidemic or vasodilating properties as does niacin. When oral therapy is precluded because of diarrhea or lack of patient cooperation, 100 to 250 mg should be injected sc bid to tid. In encephalopathic states, 1000 mg po plus 100 to 250 mg IM is recommended. Other B-complex vitamins should also be given in therapeutic dosages.

VITAMIN B_6 DEFICIENCY AND DEPENDENCY

Vitamin B_6 comprises a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized and phosphorylated in the body to pyridoxal phosphate, which functions as a coenzyme in many reactions, including decarboxylation and transamination of amino acids, deamination of hydroxyamino acids and cysteine, conversion of tryptophan to niacin, and metabolism of fatty acids. Consequently, the vitamin B_6 group is important in blood, CNS, and skin metabolism. Vitamin B_6 is important in erythropoiesis because pyridoxal phosphate is needed in the formation of δ-aminolevulinic acid, the rate-limiting step in heme biosynthesis.

Primary deficiency is rare, because most foods contain vitamin B_6. Nonetheless, an outbreak of convulsions in infants did follow the inadvertent destruction of vitamin B_6 in infant formulas. Secondary deficiency may result from malabsorption, alcoholism, oral contraceptive use, chemical inactivation by drugs (eg, isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine), excessive loss, and increased metabolic activity.

Symptoms and Signs

Deficiency: The vitamin B_6 antagonist deoxypyridoxine produces seborrheic dermatosis, glossitis, cheilosis, peripheral neuropathy, and lymphopenia. Vitamin B_6 deficiency can cause convulsions in infants and anemia in adults (usually normocytic but occasionally microcytic).

Dependency: Several recessive or X-linked states affect different vitamin B_6 apoenzymes, producing symptoms such as convulsions, mental deficiency, cystathioninuria, sideroblastic (iron overload) anemia, urticaria, asthma, and xanthurenic aciduria.

Laboratory Findings and Diagnosis

At present, there is no generally accepted test of vitamin B_6 status. The whole blood level of pyridoxal phosphate is a better indicator than the plasma level. Erythrocyte glutamic pyruvate and oxaloacetic transaminase activities are decreased in vitamin B_6 deficiency, but these changes are not diagnostic because of the wide range of values in healthy persons.

Treatment

Underlying causes such as use of pyridoxine-inactivating drugs (anticonvulsants, corticosteroids, estrogens, isoniazid, penicillamine, and hydralazine) or malabsorption should be corrected. For dependency in infants, the daily requirement (normally 0.4 mg) is increased many times (up to 10 mg). For pyridoxine-dependent seizures, the initial dose is 50 to 100 mg IM or IV daily for 1 wk followed by oral doses tapered over 1 wk to 25 mg. Deficiency in adults usually responds to pyridoxine 50 to 100 mg/day po. Conditions that increase metabolic demand, such as hyperthyroidism and diabetes, require amounts in excess of the recommended allowance. For pyridoxine deficiency associated with drugs such as isoniazid, 100 mg/day may be required. For dependency in adults, as much as 200 to 600 mg daily of pyridoxine may be needed.

VITAMIN B_6 TOXICITY

The ingestion of megadoses (2 to 6 g/day for 2 to 40 mo) of pyridoxine, mistakenly taken for premenstrual tension, may cause progressive sensory ataxia and profound lower limb impairment of position and vibration sense. Senses of touch, temperature, and pain are less affected. The motor and central nervous systems are unimpaired. Recovery is slow and, in some patients, is only partial after pyridoxine ingestion is stopped.

BIOTIN DEFICIENCY AND DEPENDENCY

Biotin functions as a coenzyme for carbon dioxide transfer and hence is essential to fat and carbohydrate metabolism. A specific enzyme links biotin to its apoenzymes.

Deficiency: Raw egg white contains a biotin antagonist, avidin. Prolonged consumption of raw egg whites may result in dermatitis and glossitis, which respond rapidly to 150 to 300 μg biotin daily. Deficiency has also occurred during long-term TPN without supplementary biotin.

Dependency: Retarded physical and mental development, alopecia, keratoconjunctivitis, and defects in T-cell and B-cell immunity have been reported in children with deficiencies of multiple biotin-dependent carboxylases. Deficiencies result from mutations in holocarboxylase synthetase (the enzyme required to link biotin to four carboxylases necessary for metabolism) or in biotinidase (the enzyme required to remove biotin from the same enzymes in catabolism). Urinary excretion of various organic acids assists diagnosis. Children with holocarboxylase synthetase and biotinidase abnormalities respond well to large doses of biotin (5 to 20 mg) daily.

PANTOTHENIC ACID DEFICIENCY

Pantothenic acid is a vitamin widely distributed in foodstuffs and is an essential component of coenzyme A, which functions as an acyltransfer cofactor for many enzymatic reactions. Adults probably require about 4 to 7 mg/day, corresponding to a whole blood level of 100 to 180 μg/dL (4.56 to 8.21 μmol/L), but no RDA has been set. Pantothenic acid deficiency is rarely observed in humans.

Adult volunteers on a deficient diet experienced malaise, abdominal discomfort, and burning feet associated with paresthesias, which responded to pantothenic acid. In

TABLE 202–1. TYPES OF DIETARY FAT

Fats	Sources
Saturated fats	Meats, non-skim dairy products, artificially hydrogenated vegetable oils
Monounsaturated fats	Olive oil, canola oil
Polyunsaturated fats	
Omega-3 oils	Sea plankton, deep-sea cold-water fatty fish (eg, tuna, salmon, mackerel)
Omega-6 oils	Cultivated vegetable oils (eg, corn oil)

Association recommends that the proportion be reduced to 30%, yet a reduction to < 10% may be needed to have a major effect on CAD risk.

The type of dietary fat is also important; there are three kinds (TABLE 202–1): saturated, monounsaturated, and omega-3 and omega-6 PUFAs. The ideal proportion of each of these fats is unknown. However, diets high in saturated fats are clearly atherogenic, and those high in monounsaturates or omega-3 oils are less so.

U.S. studies failed to show a decreased incidence of angina or MI in persons eating diets high in omega-3 oils, although such diets were associated with decreased risk of sudden cardiac death. Persons eating the most fish consumed an average of 0.58 g/day of omega-3 oils, but much higher intakes of omega-3 oils are probably needed for demonstrable risk factor reduction. For example, omega-3 oil supplementation with two or three divided doses of eicosapentaenoic acid 1.8 to 6 g/day and docosahexaenoic acid 0.75 to 2.5 g/day lowers elevated serum triglyceride levels. These doses are up to 10 times the amounts consumed by the fish eaters in the U.S. studies.

For patients at high risk of CAD and especially for those with evidence of CAD, it is reasonable to recommend a 20 g/day fat diet consisting of 6 to 10 g of PUFAs with equal proportions of omega-6 and omega-3 oils, ≤ 2 g of saturated fat, and the remainder as monounsaturates.

Fruits and vegetables: Five servings/day of fruits and vegetables, which are rich in phytochemicals, seems to decrease the risk of CAD and some cancers. However, populations eating a high phytochemical diet also tend to consume less saturated fat, more fiber, and more vitamin C and E, making the role of phytochemicals less clear. One group of phytochemicals called flavonoids (found in red and purple grapes, red wine, black teas, and dark beers) appear particularly protective against CAD. High intake of flavonoids in red wine may help explain why French populations have a relatively low incidence of CAD, despite using more tobacco and consuming more fat than Americans do.

Fiber: Americans eat relatively little fiber, of which there are two kinds: soluble fiber (found in oat bran and psyllium), which decreases total cholesterol and may have a beneficial effect on glucose and insulin levels, and insoluble fiber (eg, cellulose, lignin). Fiber is not without adverse effects, however, such as interfering with the absorption of certain minerals and vitamins. In general, foods rich in phytochemicals and vitamins are also rich in fiber.

Vegetable proteins: Consumption of vegetable proteins (eg, soy, tempeh, seitan) seems to decrease CAD risk.

DIETARY SUPPLEMENTATION

Dietary supplementation with vitamins, phytochemicals, omega-3 oils, and trace minerals remains controversial. There are data to justify supplementation with vitamin E, vitamin C, folic acid, and Ca but less convincing data to support the use of vitamin B_6 and B_{12}.

Vitamin E decreases the oxidation of serum LDL-C and thus appears to reduce its capability for vascular damage. Serum vitamin E levels are inversely correlated with incidence of cardiovascular mortality, and supplementation with vitamin E 800 IU/day has been shown to decrease the incidence of MI. A recent study among nurses showed that diets higher in vitamin E were associated with lower death rates from heart disease but failed to show a specific benefit of vitamin E supplementation, possibly because of problems with study design and data collection. Further studies are underway.

Although it has not been shown to decrease the risk of heart disease, supplementation with vitamin C 250 to 500 mg bid increases the antioxidant properties of vitamin E.

Folic acid 0.8 mg bid prevents CAD by lowering elevated levels of homocysteine. Vitamins B_6 and B_{12} also lower homocysteine levels, but evidence justifying their use in general prevention is scanty. Calcium 500 mg bid, aside from its other benefits, appears to have a role in normalizing BP in certain persons.

EXERCISE

Recent studies have shown that increased levels of physical activity and fitness are associated with a decreased incidence of heart disease and hypertension. However, there have been no controlled trials on the optimal intensity, duration, frequency, or type of exercise. Also, the question of whether people with healthy hearts choose more active lifestyles or whether active lifestyles lead to healthier hearts remains unanswered. Several controlled but small studies demonstrated beneficial effects of exercise on BP and on CAD risk.

Comprehensive cardiac rehabilitation, of which exercise is an important part, decreases long-term morbidity and mortality after MI. It is equally beneficial in patients with angina and in those who have undergone bypass surgery or angioplasty. Cardiac rehabilitation involves the same principles used in the primary prevention of CAD. However, most patients and physicians pay little attention to aggressive prevention of heart disease until signs of CAD appear.

Pre-exercise evaluation should consist of a history and physical examination to exclude such conditions as valvular heart disease, ventricular hypertrophy, dangerous arrhythmias, hypertension, exercise-induced asthma, hemoglobinopathies, and musculoskeletal disease. In adolescents or young adults without abnormal findings, no further workup is generally needed. Evaluation is more extensive in older persons and those who are sick or at increased risk of disease (including those with poorly controlled diabetes, heart disease, hypertension, or obesity). Ideally, such people should have an exercise stress test (see Ch. 198). Further evaluation (eg, by a physical therapist for patients with musculoskeletal problems) should be considered before the start of resistive strength training. Patients with elevated cholesterol levels should have lipoprotein analysis, body fat estimation, and dietary evaluation. Obese patients should have dietary analysis, thyroid function tests, and determinations of blood glucose, insulin levels (both fasting and following oral glucose) and resting metabolic rates may be evaluated in research studies.

There are three kinds of exercise programs: those that promote endurance, muscle strength, and flexibility. Endurance and muscle strength have a clear role in CAD prevention. Any complete exercise program should include all three kinds. The American College of Sports Medicine has established minimum exercise recommendations for healthy men and women of all ages to develop and maintain cardiorespiratory fitness, healthy body composition, and muscular strength and endurance (see TABLE 202–2).

Components of endurance exercise include duration, frequency, type, and intensity. Endurance training should last ≥ 40 min/day at least three times/wk. Each ses-

TABLE 202–2. AMERICAN COLLEGE OF SPORTS MEDICINE MINIMUM EXERCISE RECOMMENDATION

Parameter	Recommendation
Frequency	3–5 days/wk
Intensity	To 60–90% of maximum heart rate or to a heart rate at 50–85% of maximum O_2 uptake or heart rate reserve
Duration	20–60 min of continuous aerobic activity depending on intensity
Method	Should use large muscle groups, can be maintained continuously, and is rhythmical and aerobic (eg, walking/hiking, running/jogging, cycling, cross-country skiing, dancing, skipping rope, rowing, stair climbing, swimming, skating)
Resistive strength training	At least one set of 8–12 repetitions of 8–10 exercises that condition the major muscle groups at least twice/wk

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Recommended for Adoption
at Step 4 of the ICH Process
on 6 February 2003
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Excipient
Anything other than the drug substance in the dosage form.

Expiration date
The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies
Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers
Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate testing
Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long term testing
Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Mass balance
The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing
The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature
A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.*, 60:927-929, 1971) can be used.

New molecular entity
An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of

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Butterworths Medical Dictionary

Second Edition

Editor-in-Chief
Macdonald Critchley

Ewing's sign. Tenderness of the medial part of the floor of the frontal air sinus elicited by digital compression, and suggestive of sinus infection.

ex-. 1. Prefix, from the Latin *ex*, meaning *from, out of, without*. 2. Prefix, from the Greek *ex*, meaning *out*.

exacerbation (ex·as·er·ba'·shun). Increase in severity of a disease or in violence of symptoms. [L *exacerbare* to irritate intensely.]

exaemia (ex·e·me·ah). A condition in which a considerable quantity of blood is temporarily removed from general circulation, as in shock when blood accumulates in the abdomen, or when a limb is ligatured. [Gk *ex*, *haima* blood.]

exaltation (ex·awl·ta·shun). 1. Abnormal intensification of organic or functional power. 2. Abnormal increase in mental activity. 3. In psychological medicine, exaggerated sense of personal well-being and power, with spiritual ecstasy and delusions of grandeur. [L *exaltare* to raise high.]

examination (ex·am·in·a'·shun). Critical investigation and inspection for diagnostic purposes.

exangeia, exangia (ex·an·je·ah). A state of dilatation of a blood vessel. [Gk *ex*, *aggeion* vessel.]

exanimation (ex·an·im·a'·shun). 1. A state of unconsciousness or coma. 2. A state of fainting. 3. Death. [L *ex*, *animus* soul.]

exanthem (ex·an·them). The rash or eruption produced by the action of an organism or its toxins on the small blood vessels of the skin. **Boston exanthem.** A febrile illness with a macular exanthem and, sometimes, an oral enanthema, caused by *Echovirus 16*. [Gk *ex*, *anthema* blossoming.]

exanthema (ex·an·the·mah) (pl. *exanthemata*). One of a group of infectious diseases in which a specific rash is an important clinical feature and may assist diagnosis. **Exanthema subitum.** Pseudorubella: an eruptive disease resembling rubella in its rash, the enlargement of glands of the neck, and fever, but differing from it in its age incidence, which is exclusively from 6 months to 2 years. The rash fades in 2 or 3 days, and there are no sequelae. Leucopenia with marked relative lymphocytosis may help in diagnosis. [see prec.]

exanthematous (ex·an·them·at·us). 1. Belonging or relating to or having the characteristics of an exanthem. 2. Showing the character of an eruptive disease.

exanthesis (ex·an·the·sis). Any eruption of the skin; an exanthem. **Exanthesis rosalia arthrodynia.** Dengue. [Gk a blossoming.]

exanthrope (ex·an·thrope). Any source outside the human body that gives rise to disease. [Gk *ex*, *anthropos* man.]

exanthropia (ex·an·thro·pe·ah). Morbid aversion to and avoidance of human society. [see prec.]

exanthropic (ex·an·throp·ik). 1. Referring to an exanthrope or exanthropia. 2. Originating outside of or not existing within the human body.

exarteritis (ex·ar·ter·i'·tis). A condition of inflammation of the tunica adventitia of an artery. [Gk *ex*, artery, Gk *-itis* inflammation.]

exarthrima (ex·ar·thrim·ah). Dislocation of a joint. [Gk *ex*, *arthron* joint.]

exarticulation (ex·ar·tik·ew·la'·shun). 1. Dislocation. 2. Amputation of a limb through a joint. 3. Excision of a part of a joint. [L *ex*, *articulatio* joint.]

excalation (ex·kal·a·shun). The exclusion or suppresion of one or more parts or members of a series, as a digit or a vertebra. [L *ex*, *calare* to call.]

excavation (ex·kav·a·shun). The process of scooping out. **Dental excavation.** The process of removing caries from a cavity in a tooth by means of an excavator. **Excavation of the optic disc.** Pallor and hollowing-out of the nerve head; also called *cupping*. It may be *physiological*, confined to the centre of the disc; *glaucomatous*, extending to the edge of the disc and often deep with overhanging edges; *postatrophic*, shallow and saucer-like; or *cavernous*, very deep and thought to be arteriosclerotic in nature, as it is not associated with raised tension. **Excavation of the disc of the optic nerve** [excavatio disci (NA)]. The depression at the entry of the optic nerve into the retina; sometimes also termed the *physiological cup*. [L *ex*, *cavus* hollow.]

See also: SCHNABEL.

excavator (ex·kav·a·tor). 1. A large sharp spoon or scoop used to clear a cavity of morbid tissue. 2. In dentistry, an instrument used to clear out a tooth cavity preparatory to the insertion of a filling. **Spoon excavator.** A spoon-shaped dental excavator. [see prec.]

excentric (ek·sen·trik). 1. Eccentric. 2. Away from the centre or the median line. 3. Efferent. [L *ex*, centre.]

excerebration (ek·ser·e·bra'·shun). 1. In obstetrics, removal of the fetal brain in the operation of embryotomy. 2. Removal of the brain in dissection. [L *ex*, cerebrum.]

excess (ek·ses). Departure from normal. **Base excess.** Base concentration per litre of blood measured by acid titration to pH 7.4. **Convergence excess.** A form of muscle imbalance in which there is a tendency to converge, which is more marked for near vision than for distance. [L *excedere* to go out.]

exchange (ex·cha·n)). In cytogenetics, denoting chromosome mutations due to exchange of segments between chromatids of the same chromosome (*intrachange*) or between different chromosomes (*interchange*). [L *ex-*, *cambire* to change.]

excipient (ek·sip·e·ent). A binding agent enabling powdered drugs to be made into pills. Among the liquid excipients are syrup of glucose, mucilage of acacia and simple sugar; among the solids are gum acacia, liquorice, powdered soap and a mixture of gum acacia and tragacanth. Excipients must not have therapeutic action of their own, nor should they be of such a nature as to render the resultant pill insoluble. Colour must also be taken into account, and a white excipient used with white ingredients of a pill. [L *excipere* to take up.]

excise (ek·size). 1. To hollow out. 2. To amputate. 3. To cut away as diseased matter from healthy matter. [L *ex*, *caedere* to cut.]

excision (ek·sizh·un). The act or operation of excising or amputating a part. **Excision of a wound, Wound excision.** Débridement. [see prec.]

See also: LOCKHART-MUMMERY.

excitability (ek·si·tab·il'·it·e). 1. Irritability. 2. A property of living organisms causing them to respond quickly to the action of stimulants or a stimulus. [L *excitare* to rouse.]

excitable (ek·si·tabl). 1. Responding rapidly to stimulus. 2. Capable of being stimulated or excited. [see prec.]

excitant (ek·si·tant). 1. Tending to stimulate. 2. Any agent that stimulates or augments organic activity. 3. Any agent or remedy that stimulates mental function or the vital functions. [see foll.]

excitation (ek·si·ta·shun). 1. A state of being mentally or nervously excited. 2. The condition of being stimulated. 3. The act of increasing the rapidity or the intensity of a process. 4. In physics, the addition of energy to a system, transforming it from its ground state to an excited state. **Anomalous atrioventricular excitation.** Pre-excitation. Wolff-Parkinson-White syndrome. **Direct excitation.** Muscular stimulation brought about by placing an electrode on the muscle itself. **Indirect excitation.** The act of stimulating a muscle by stimulating its nerve. [L *excitare* to rouse.]

excitatory (ek·si·ta·tor·e). 1. Tending or serving to excite or stimulate. 2. Tending to induce disassimilation. [see prec.]

excitement (ek·site·ment). The second stage of anaesthesia. [L *excitare* to rouse.]

excito-anabolic (ek·si·to·an·ab·ol'·ik). Stimulating the process of anabolism. [excitation, anabolism.]

excitocatabolic (ek·si·to·kat·ab·ol'·ik). Stimulating the process of catabolism. [excitation, catabolism.]

excitoglandular (ek·si·to·glan'·dew·lar). Stimulating activity of a gland. [excitation, gland.]

excitometabolic (ek·si·to·met·ab·ol'·ik). Stimulating the activity of the metabolic process; giving rise to changes in metabolism. [excitation, metabolism.].

excitomotor, excitomotory (ek·si·to·mo'·tor, ek·si·to·mo'·tor·e). 1. Producing or increasing rapidity of movement. 2. Promoting motor function. 3. Any agent, e.g. a drug, that excites or induces functional or nervous activity or movement. [excitation, motor.]

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Definition of Frequently Used Terms in Regulatory Affairs and Quality Assurance

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Abstract. *The following is a list of terms frequently used in Regulatory Affairs and Quality Assurance, along with their definitions.*

- **Acceptance Criteria** – Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

- **Accuracy** – The "closeness" of the test results obtained by an analytical method to the true value.

- **Active Pharmaceutical Ingredient** – See "Drug Substance."

- **Animal Pharmacology/Toxicology Studies** – Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.

- **Batch** – A specific quantity of an intermediate or drug substance intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture. A batch may also mean a specific quantity of material or drug substance processed in one process or series of processes so that it could be expected to be homogenous.

- **Calibration** – The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system and the corresponding known values of the measurement.

- **Clinical Investigator Information** – Information on the qualifications of clinical investigators/professionals (generally physicians) who oversee the administration of the experimental compound to assess whether they are qualified to fulfill their clinical trial duties.

- **Clinical Protocols** – Detailed protocols for proposed clinical studies to assess whether the initial phase trials will expose subjects to unnecessary risks.

- **Combination Product** – A drug product that contains more than one drug substance.

- **Compliance Verification Report (CVR)** – A report issued by the Product Information Management Branch of the FDA to all firms that have at least one prescription product listed with the FDA in order to assist with drug product listing requirements.

- **Concurrent Validation** – A subset of prospective validation in which API batches are released for distribution, based on extensive testing, before completion of process validation. Once data from additional batches produced under replicated conditions show uniformity, the process may be considered validated.

- **Controlled Substance** – A drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of Part B of 21 USCS Section 812 (United States Code Service). This term does not include distilled spirits, wine, malt beverages, or tobacco.

- **Counterfeit Substance** – A controlled substance which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, number, or device, or any likeness thereof, of a manufacturer, distributor, or dispenser other than the person or persons who in fact manufactured, distributed, or dispensed such substance and which thereby falsely purports or is represented to be the product of, or to have been distributed by, such other manufacturer, distributor, or dispenser.

- **Debarment** – The act of excluding an individual that has been convicted of a crime under federal law for conduct relating to the development or approval of any drug product or otherwise relating to the regulation of any drug product under the Federal Food, Drug, and Cosmetic Act, from providing services in any capacity for the submission, or assisting in the submission, of any approved or pending drug product application.

- **Degradation Product** – A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called *Decomposition Product.*

- **Design Qualification (DQ)** – Defines the functional and operational (or performance) specifications for any piece of equipment and any ancillary systems.

- **Drug** – As defined in Section 201 (g)(1) of the Food, Drug, and Cosmetic Act means (a) articles that are recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to them; (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals; and articles (other than food) intended to affect the structure or any function of the body of humans or other animals.

- **Drug Product** – A finished dosage form (e.g. tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients. Includes human drugs, veterinary drugs, and medical animal feed premixes which includes biological products, but does not include blood and blood components.

- **Drug Substance** – An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body, but does not include intermediates used in the synthesis of such ingredient.

- **Excipient (ICH Q1A)** – Anything other than the drug substance in the dosage form.

- **Expiry/Expiration Date (ICH Q1A)** – The date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used.

- **Extractables/Leachables** – Materials or components derived from the container/closure which have been transferred into the contained drug substance of drug product.

- **FDA 482** – A written, signed Notice of Inspection issued to a firm by an FDA Investigator who has the authority to enter and inspect a firm operating at a business location. A FDA 483 may be issued as a result of the inspection.

- **FDA 483** – A listing of observations of objectionable conditions and practices, pursuant to Section 704(b) of the Federal Food, Drug, and Cosmetic Act, to assist firms in complying with the Acts and regulations enforced by the Food and Drug Administration. This listing is presented to the highest management official available upon completing an inspection and before leaving the premises.

- **Final Intermediate** – The last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance must involve covalent bond formation; ionic bond formation (i.e. making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

- **Final Solution Step** – The solution from which the drug substance is isolated in pure form by either crystallization or precipitation. Where the purification procedure for the crude drug substance involves several crystallization or precipitation steps, final solution step refers only to the last of these steps.

- **Firm** – A company engaged in the manufacture, preparation, propagation, compounding, or processing of a drug product.

- **Historical Data** – Data on impurities or physical attributes from ten recent batches representative of the established process. The upper statistical limit of an impurity is generally based on the mean plus three times the standard deviation. [The appropriate review division(s) should be contacted for concurrence in those rare instances (e.g., low-volume drug substances) where evaluation of historical data is based on <10 batches.]

- **Identified Impurity** – An impurity for which a structural characterization has been achieved.

- **Impurity** – Any component of the drug substance that is not the entity defined as the drug substance (ICH Q3A).

- **Impurity Profile** – A description of the identified and unidentified impurities present in a drug substance (ICH Q3A).

- **In Situ Intermediate** – An intermediate that is not isolated. It is normally, but not necessarily, in solution (*Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*).

- **Installation Qualification (IQ)** – The documented verification that all key aspects of the equipment and ancillary systems installations adhere to the approved design intentions (plans) and that the recommendations of the manufacturer are suitably considered.

- **Instrument Testing** – The process of executing experiments to measure the performance characteristics following documented procedures.

- **Intermediate** – A material produced during steps in the synthesis of an active pharmaceutical ingredient that must undergo further molecular change or processing before it becomes an active pharmaceutical ingredient.

- **International Conference on Harmonization (ICH)** – A project combining the regulatory authorities of Europe, Japan, and the United States, as well as experts in the Pharmaceutical Industry in these three regions, to discuss scientific and technical aspects of product registration. The purpose of the ICH is achieving greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of this harmonization is a more economical use of human, animal, and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory observations to protect public health.

- **Isolated Intermediate** – An intermediate that is obtained as the product after work-up of a reaction step in the synthetic scheme for the drug substance. The isolation or purification procedure should be part of the validated process. An aliquot of a reaction product that is worked-up and/or purified for purposes of characterization does not constitute an isolated intermediate.

- **Justification** – Reports containing scientific data and expert professional judgment to substantiate decisions (*SUPAC IR, Immediate Release Solid Oral Dosage Forms, Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation).*

- **Limit of Detection (LOD)** – The lowest amount of test material in a sample that can be detected but not necessarily quantified.

- **Limit of Quantitation (LOQ)** - The lowest amount of test material in a sample that can be quantitatively determined.

- **Linearity** – An analytical methods ability to obtain results that are directly proportional to the concentration of the test material in the sample.

- **List I Chemical** – A chemical specified by regulation of the Attorney General as a chemical that is used in manufacturing a controlled substance in violation of Title 21 USCS Section 812 and is important to the manufacture of the controlled substance.

- **Listing Requirements** – All firms, unless exempted, are requested to list their commercially marketed drug products with FDA within 5 days after the beginning of operation. They are required to list/update their drug products listing twice a year.

- **Lot** - A batch, or a specific identified portion of a batch having uniform character and quality within specified limits. For an active pharmaceutical ingredient produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

- **Lot Number (Control Number or Batch Number)** – Any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of an active pharmaceutical ingredient or other material can be determined.

- **Manufacturing/Processing** – Repackaging or otherwise changing the container, wrapper, or labeling of any drug product package in the distribution process from the original producer to the ultimate consumer.

- **Manufacturing Information** – Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and drug product. This information is assessed to insure the company can adequately produce and supply consistent batches of the drug.

- **Method Validation** – The process of proving that an analytical test procedure is effective for its intended use.

- **New Molecular Entity** – The designated therapeutic moiety (active pharmaceutical ingredient) in a dosage form that has not been approved for marketing in the United States (also referred to as a new chemical entity or new drug substance). It may be a complex, simple ester, or salt of a previously approved active chemical ingredient.

- **Operational Qualification (OQ)** – The documented verification that the equipment and ancillary systems perform as intended throughout anticipated operating ranges (i.e., pressures, temperatures, times).

- **Performance Qualification** – The documented verification that the equipment and ancillary systems will function according to a specification appropriate to its routine use.

- **Pilot-Plant Scale** – The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale.

- **Pilot Scale** – The manufacture of a bulk drug substance or intermediate on a reduced scale by processes representative of and simulating that to be applied on a larger, commercial manufacturing scale.

- **Polymorphism** – The occurrence of different crystalline forms of the same drug substance (ICH Q3A). This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

- **Precision** – The degree of agreement of individual test results when an analytical procedure is applied repeatedly to multiple samplings of a homogenous sample (usually expressed as a standard deviation).

- **Production Batch** – A batch of a drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

- **Process Validation** – Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics.

- **Product Information Management Branch (FDA)** – Assists firms with mandatory updates of their drug product listings.

- **Prospective Validation** – Establishing documented evidence that a system does what it purports to do prior to the commercial distribution of a new active pharmaceutical ingredient or an existing active pharmaceutical ingredient made by a new or modified process.

- **Qualification** – The action of proving that any equipment or process works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process, i.e., installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

- **Quality** – The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity of the article.

- **Quality Assurance** – The sum total of the organized activities performed with the intent to ensure that all active pharmaceutical ingredients are of the quality required for their intended use.

- **Quality Control Unit** – Any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

- **Range** – The upper and lower limits (inclusively) of the test material for which an analytical method can perform with precision, accuracy, and linearity.

- **Raw material** – Any ingredient intended for use in the production of active pharmaceutical ingredients. These may include starting materials, process aids, solvents, and reagents.

- **Reagent** – A substance, other than a starting material or solvent, that is used in the manufacture of a drug substance.

- **Reference Standard** – A particular lot or batch of drug substance specifically prepared, either by independent synthesis or by additional purification of production material, and shown, by an extensive set of analytical tests, to be authentic material of the highest purity reasonably attainable.

- **Registration Exemption** – Pharmacies, hospitals, and clinics that dispense drug product at retail; licensed physicians who use drug products solely for purposes related to their professional practice; and/or persons using drug products solely for their professional needs and are not for sale are exempt from registration.

- **Registration Process** – Firms can register with the FDA by obtaining a Registration of Drug Establishment Form within five days after the beginning of operation or submission of an application. Firms are required to re-register annually by returning an Annual Registration of Drug Establishment Form within 30 days after receiving it from the Product Information Management Branch.

- **Registration Requirements** – A firm must register all drug products (Domestic Manufacturers, Domestic Repackers, Domestic Labelers, and submissions for New Human Drug Application, New Animal Drug Application, Medicated Feed Application, Antibiotic Drug Application, and Establishment License Application to Manufacture Biological Products) whether or not they enter interstate commerce. All domestic distributors and foreign firms importing drug products into the United States must obtain a labeler code and list all of their products.

- **Reprocessing** – Introducing an intermediate or active pharmaceutical ingredient that does not conform to standards or specifications, back into the process and repeating one or more steps that are part of the established manufacturing process (e.g., recrystallization using the same solvent).

- **Retest Date (ICH Q1A)** – The date when samples of the drug substance should be reexamined to ensure that the material is still suitable for use.

- **Retest Period** – The period of time during which the active pharmaceutical ingredient can be considered to remain within specifications, and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under defined conditions. After this period, the active pharmaceutical ingredient should be retested for compliance with specifications before use.

- **Retrospective Validation** – Establishing documented evidence that a system does what it purports to do based on a review and analysis of historic information. It is normally conducted on an active pharmaceutical ingredient already being commercially distributed and is based on accumulated production, testing, and control data.

- **Reworking** – Subjecting an intermediate or active pharmaceutical ingredient that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process (e.g., recrystallizing with a different solvent).

- **Ruggedness** – A measure of the lack of influence on test results of operational and environmental variables of an analytical method. Also defined as the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of test conditions.

- **Schedule I Controlled Substance** – A drug or other substance which has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and for which there is a lack of accepted safety for use of the drug or other substance under medical supervision.

- **Schedule II Controlled Substance** – A drug or other substance which has a high potential for abuse, has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and for which abuse of the drug or other substance may lead to severe psychological or physical dependence.

- **Schedule III Controlled Substance** – A drug or other substance which has a potential for abuse less than the drugs or other substances in Schedules I and II, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

- **Schedule IV Controlled Substance** – A drug or other substance which has a low potential for abuse relative to the drugs or other substances in Schedule III, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

- **Schedule V Controlled Substance** – A drug or other substance which has a low potential for abuse relative to the drugs or other substances in Schedule IV, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

- **Selectivity** – The ability of a testing procedure to measure a test material in the presence of additional components that may be present in the sample matrix which could potentially interfere with the analytical method.

- **Semisynthetic Drug Substance** – A drug substance produced by fermentation and synthesis or synthesized from a precursor or structural element of natural origin (e.g., a natural product of natural or plant origin).

- **Shelf Life; Expiration Dating Period** – The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed container and closure.

- **Solvent** – An inorganic or an organic liquid used as the vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

- **Specification** – A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. *Conformance to specifications* means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant (ICH draft guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

- **Specific Test** – A test that is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

- **Specified Impurity** – An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

- **Stability** – The capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.

- **Stability–Indicating Methodology** – Validated quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.

- **Starting Material** – A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an intermediate and/or of the drug substance. Starting materials are usually available from commercial sources, and their chemical and physical properties, structure, and impurity profile are well defined in the chemical literature.

- **Testing** – A technical operation that consists of the determination of one or more characteristics or performance of a given product, material, equipment organism, physical phenomena, process, or service according to a specified procedure.

- **Testing Requirements** – Test conditions and standard operating procedures with clear instructions describing how to perform the tests and how to evaluate the results.

- **Theoretical Yield** – The quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular active pharmaceutical ingredient or intermediate, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

- **Total Impurities** – The sum of all impurities observed above the limit of quantitation.

- **Unidentified Impurity** – An impurity that is defined solely by qualitative analytical properties (e.g. chromatographic retention time).

- **Universal Test** – A test that is considered to be potentially applicable to all new drug substances or all new drug products (e.g. appearance, identification, assay, and impurity tests).

- **Validation** – Establishing documented evidence that provides a high degree of assurance that a system, method, or operation does what it is supposed to do, reliably and consistently.

- **Validation Protocol** – A written plan stating how validation will be conducted and identifying specific acceptance criteria. For example, the protocol for a typical manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling and test data to be collected, number of validation runs, and acceptable test results.

- **Verification** – Confirmation by examination and provision of evidence that specified requirements have been met.

- **Warning Letter** – A written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act, or other Acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation, may result in administrative and/or regulatory enforcement action without further notice.

- **Working Standard** – An active pharmaceutical ingredient, intermediate or other substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference for routine laboratory analysis.